



Specialty Board Review

Dermatology

A Pictorial Review

SECOND EDITION



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ASRA ALI

McGraw-Hill
SPECIALTY BOARD REVIEW

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PREFACE

Dermatology is a specialty that addresses both medical diseases and cosmetic problems of the skin, scalp, hair, and nails. It is a specialty that oftentimes allows the practitioner to make a diagnosis based solely on physical examination and history. Because skin symptoms and signs account for 10% of all symptoms and signs, understanding of dermatology is required of many medical specialties, particularly internal medicine, family practice, pediatrics, neurology, and rheumatology.

Initially, this book was designed to prepare dermatology residents and practicing dermatologists for the dermatology

boards and dermatology recertification exam. However, as the book has developed, it has become a comprehensive source of information on dermatologic presentations, diseases, and cosmetic and surgical procedures. Therefore, the book will not only be helpful to dermatology residents and practicing dermatologists, but also to physicians in other fields of medicine.

The second edition has been updated to keep the review current. Questions and answers were also added in order to make the learning process more interactive. I hope you will find this review as useful and informative and learn as much from it as I did while making it.

CHAPTER 1

HAIR FINDINGS

PARADI MIRMIRANI

DEVELOPMENT

- Follicles form during 3rd month of gestation; form first on head
- Lining of follicle = ectodermal origin
- Dermal papilla = mesodermal origin
- Epidermal invaginations occur at an angle to the surface and over sites of mesenchymal cell collections
- Eventually these epidermal cells form a column that surrounds the mesenchymal dermal papilla to form the bulb
- The dermal papilla (along with “stem” cells in the bulge) induce hair follicle formation by the overlying epithelium
- Additionally, two or three other collections of cells form along the follicle
 - Upper collection becomes the mantle from which the sebaceous gland will develop
 - Lower swelling becomes the attachment for the arrector pili muscle and where follicle germinal cells reside in telogen phase
 - If a third collection of cells exists, it is found opposite and superior to the sebaceous gland and develops into the apocrine gland

STRUCTURE (FIG. 1-1)

- Longitudinal structure: (superior to inferior)
 - Permanent portion of the hair follicle
 - Infundibulum
 - Area of the sebaceous gland
 - Isthmus: begins at sebaceous gland and ends at the bulge (site of insertion of arrector pili muscle)
 - Area of the bulge: location of follicular stem cells
 - Transient portion of the hair follicle
 - Lower hair follicle

- Hair bulb: contains the matrix, melanocytes; envelopes the dermal papilla; critical line of Auber is at the widest diameter; below this line is the bulk of mitotic activity

MICROSCOPIC STRUCTURE (FIG. 1-2)

- The hair follicle is arranged in concentric circles (from outer to inner)
 - Basement membrane (glassy membrane): PAS-positive, acellular; thin during anagen and thickens during catagen
 - Outer root sheath (ORS): present the length of the follicle; never keratinizes; stays fixed in place
 - Inner root sheath (IRS): grows toward cell surface and separates from the hair shaft at the level of the sebaceous gland
 - Henle’s layer: one cell thick and first to cornify
 - Huxley’s layer: two cells thick; eosinophilic-staining trichohyalin granules
 - Cuticle
- Hair shaft: grows toward cell surface; cornifies without trichohyalin or keratohyalin granules
 - Cuticle: shingle-like hair cells that interlock with cuticle cells of IRS
 - Cortex: arises from cells in center of hair bulb; disulfide bonds in this region give hair its tensile strength; keratinizes to form shaft; contains pigment of hair
 - Medulla: contains melanosomes; found only in terminal hairs
- Hair cycle: follicles (Fig. 1-1) cycle in a mosaic pattern (adjacent hairs in different stages)
 - Anagen: growth phase, stages I–VI
 - 84% of hair follicles at any one time; last a few months to 7 years
 - Cells in the hair bulb are actively dividing
 - Catagen: transitional or degenerative stage
 - 2% of hair follicles at any one time

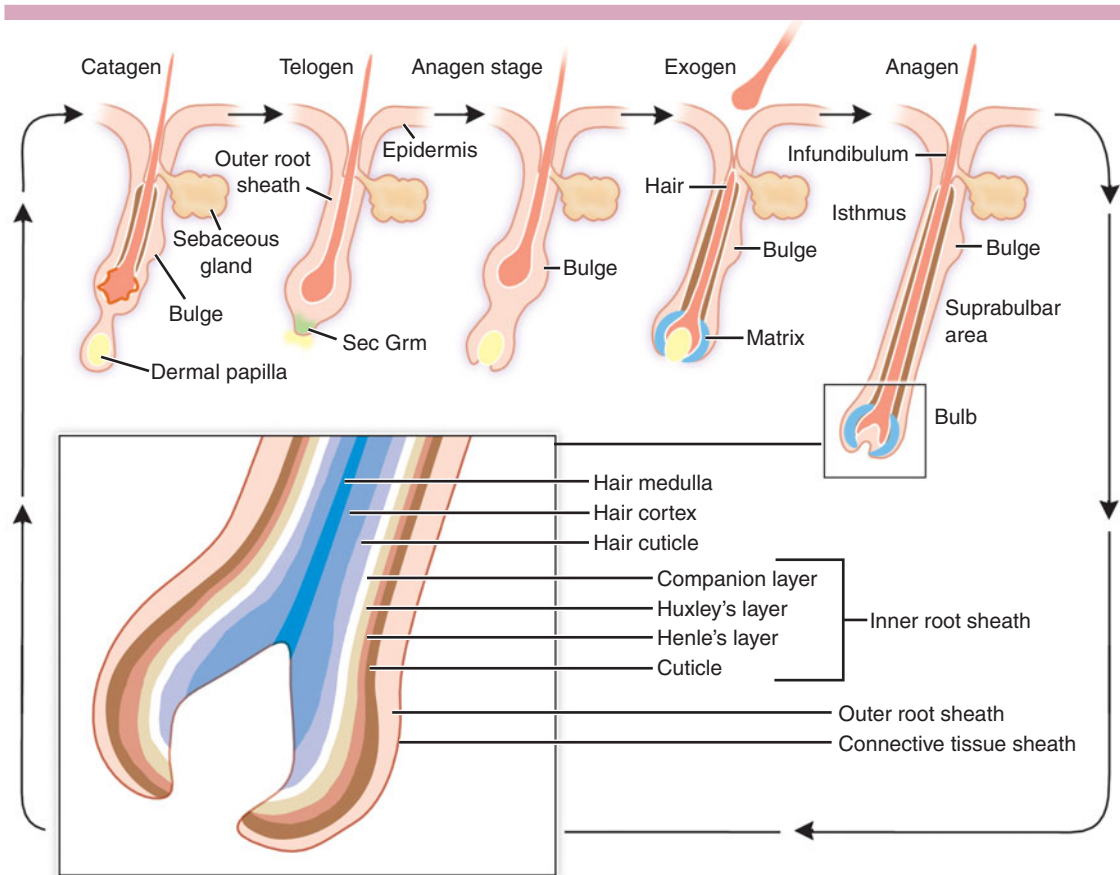


FIGURE 1-1 Hair cycle and anatomy. The hair follicle cycle consists of stages of rest (telogen), hair growth (anagen), follicle regression (catagen), and hair shedding (exogen). The entire lower epithelial structure is formed during anagen and regresses during catagen. The transient portion of the follicle consists of matrix cells in the bulb that generate seven different cell lineages, three in the hair shaft and four in the inner root sheath. (Reprinted with permission from Wolff K et al., *Fitzpatrick's Dermatology in General Medicine*, 7th edition, New York: McGraw-Hill, 2007.)

- Last a few days to weeks
- Matrix cells have stopped dividing
- Incomplete keratinization
- Thickened basement membrane (glassy layer)
- Transient, lower portion of follicle is broken down
- Telogen: resting phase
 - 14% of hair follicles at any one time
 - Last about 3 months
 - “Club hair”; no inner root sheath
 - Dermal papilla retracted to higher position in dermis
- Hair pigmentation
 - Pigment comes from melanocytes located in the matrix, above the dermal papilla
 - Eumelanin: pigment of brown-black hair
 - Pheomelanin: pigment of blonde-red hair
- Loss of melanocytes causes graying of hair—poliosis (can be seen in regrowth of hair after alopecia areata)
- Hair growth
 - Hair grows approximately 0.35–0.37 mm/day
 - Longer anagen phase = longer hair

HAIR DISORDERS

Alopecia, Nonscarring

1. Androgenetic alopecia
 - Hereditary thinning in genetically susceptible men and women
 - Circulating testosterone (T) is converted to dihydrotestosterone (DHT) by 5-alpha-reductase enzyme at the target tissue

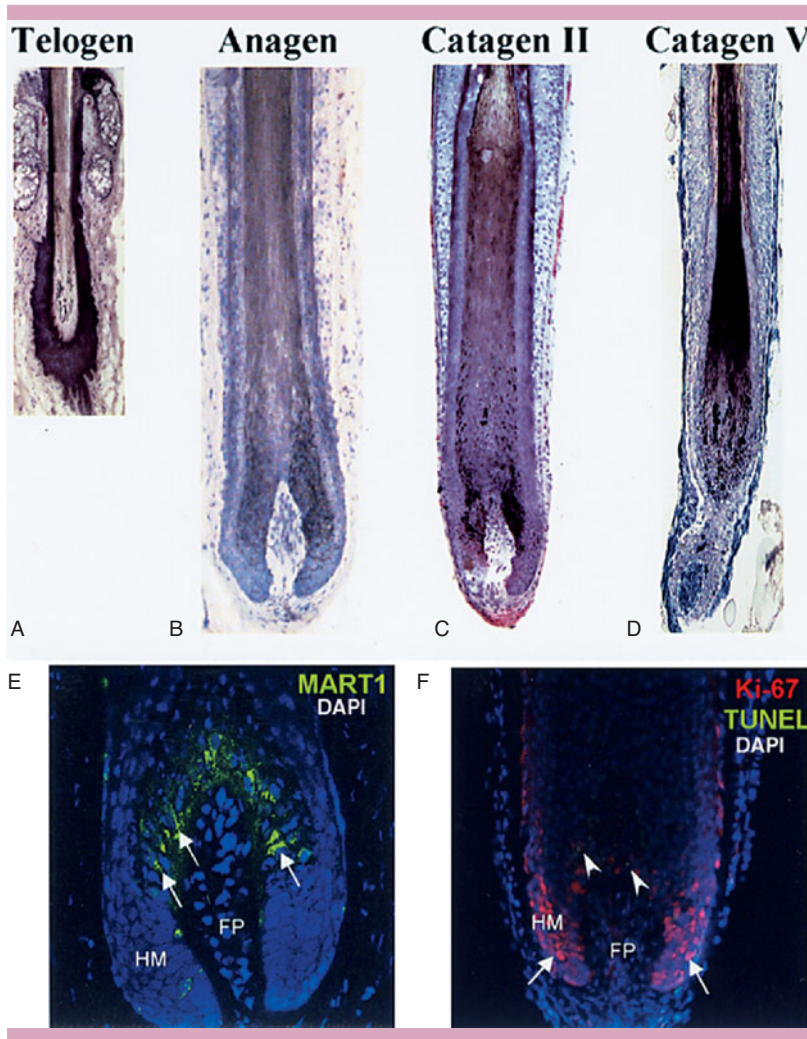


FIGURE 1-2 Morphology and fluorescent microscopy of human hair follicle at distinct hair cycle stages. **A–D.** Morphology of human hair follicle during telogen (**A**), late anagen (**B**), and early and late catagen (**C, D**). **E.** Immunofluorescent visualization of the melanocytes (arrows) in the hair bulb of late anagen hair follicle with anti-melanoma-associated antigen recognized by T cells antibody. **F.** Immunofluorescent detection of proliferative marker Ki-67 (arrows) and apoptotic TUNEL+ cells (arrowheads) in early catagen hair follicle. FP = follicular papilla; HM = hair matrix. (Reprinted with permission from Wolff K et al., *Fitzpatrick's Dermatology in General Medicine*, 7th edition, New York: McGraw-Hill; 2007.)

- DHT is the active androgen causing miniaturization of hairs in androgen sensitive areas of scalp. Anagen is shorter; number of follicles remains the same. Paradoxically DHT enlarges hair in androgen sensitive areas (beard, chest)
 - Male pattern: potential areas of hair loss are the frontal, temporal, midscalp and vertex regions (Hamilton-Norwood classification) (Fig. 1-3)
 - Female pattern: diffuse thinning in the midscalp, vertex, and temporal areas; frontal hairline is retained (Ludwig classification;)
 - Histology: miniaturization increased vellus-to-terminal-hair ratio, preserved sebaceous glands
 - Medical treatment:
 - Finasteride: 5- α -reductase type II inhibited
 - Minoxidil: increases the number of follicles in anagen, enlarges miniaturized hairs
 - Surgical treatment: hair transplantation with minigrafts and micrografts
2. Alopecia areata (Fig. 1-4)
 - Abrupt onset
 - Patchy non-scarring hair loss
 - Exclamation-point hairs which are broken hairs that are tapered at the scalp (Fig. 1-5)
 - Pigmented hair affected first, subsequently grey hair may also be targeted
 - Peach or salmon colored scalp
 - Hair pull test positive for telogen hairs when disease is active
 - Follicular damage in anagen; then rapid transformation into telogen
 - Alopecia totalis: total scalp hair loss
 - Alopecia universalis: total scalp and body hair loss
 - Ophiasis: localized hair loss along the periphery of the scalp
 - Nails: pitting, mottled lunula, trachyonychia, or onychomadesis
 - Histology: peribulbar infiltrate of T cells and macrophages (“swarm of bees”)

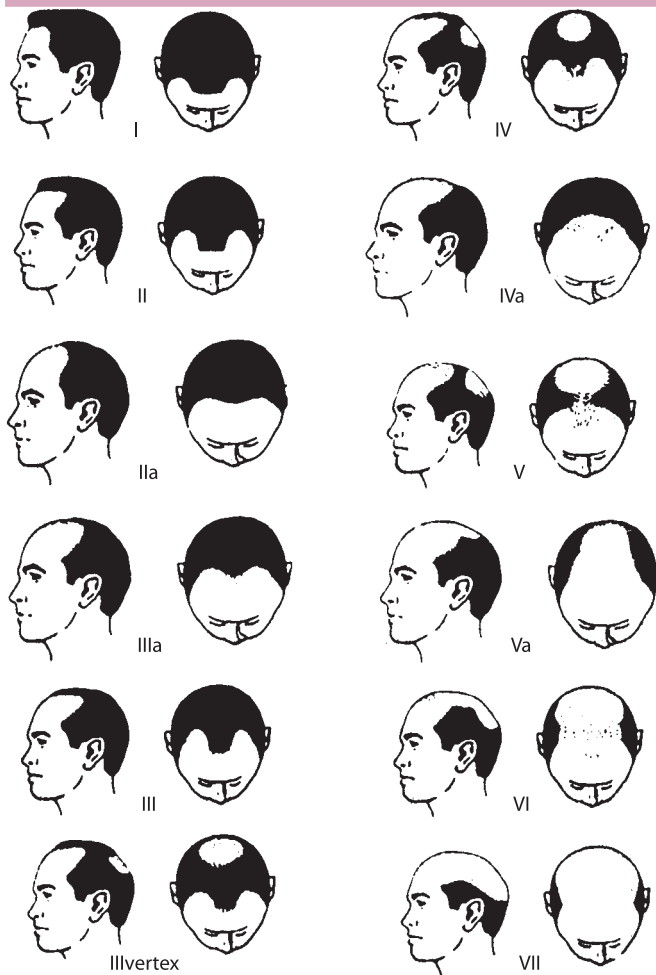


FIGURE 1-3 Androgenetic alopecia, typical male pattern.

- Associations: In the patient: atopic disorders, thyroid disease, vitiligo. In the family: atopic disorders, thyroid disease, vitiligo, diabetes mellitus, pernicious anemia, systemic lupus erythematosus (other autoimmune conditions)
 - Treatment: Patchy, or < 50%: intralesional steroids, minoxidil 5% solution, anthralin, topical steroids. Unresponsive or extensive: topical immunotherapy [squaric acid dibutylester (SADBE) or diphencyprone (DPCP)], psoralen plus ultraviolet A (UV-A), prednisone, cyclosporine
3. Telogen effluvium
- Hair shedding, often with an acute onset
 - Reactive process response to a physical event (surgery, pregnancy, thyroid disease, iron deficiency, high fever), medications (Table 1-1), or severe mental or emotional stress
 - A large number of hairs shift from anagen to telogen at one time



FIGURE 1-4 Alopecia areata. (Courtesy of Dr. Asra Ali.)



FIGURE 1-5 Exclamation point hairs in alopecia areata. (Courtesy of Dr. Paradi Mirmirani.)

- Telogen hairs move back to anagen in 3–4 months following the inciting event; hair density may take 6–12 months to return to baseline
 - The percentage of hairs in telogen rarely goes beyond 50%
 - Positive pull test: more than 6 telogen hairs
 - Telogen hairs on hair mount (Fig. 1-6)
 - Histology: increased number of telogen hairs
 - Prognosis: Recovery is spontaneous and occurs within 6 months if inciting cause is reversed. Regrowing hairs with tapered or pointed hairs can be seen in the recovery phase
4. Loose anagen syndrome
- Fair-haired children with thin, sparse, hair; no need for haircuts; easily dislodgable hair

TABLE 1-1 Common Medications Causing Telogen Effluvium

Anticancer
Anticoagulation (heparin and coumadin)
Anticonvulsant (sodium valproate, carbamazepine)
Tricyclic antidepressants and other psychiatric (amitriptyline, doxepin, haloperidol, lithium, haloperidol)
Antigout (probenecid, allopurinol)
Antithyroid (methimazole, propylthiouracil)
Beta-blockers (propranolol, timolol)
Antibiotics (nitrofurantoin, sulfasalazine)
Other (indomethacin, vitamin A)

- Examination reveals sparse growth of thin, fine hair and diffuse or patchy alopecia
 - Anagen hairs are easily and painlessly pulled from scalp
 - Diagnosis: Epilated hairs are predominantly in anagen phase; hair mount shows distorted anagen bulb, ruffled cuticle (Fig. 1-7)
 - Histology: premature and abnormal keratinization of the inner root sheath
 - Improves with age
5. Anagen effluvium (aka anagen arrest)
- Hair broken off and not shed
 - Radiation therapy and chemotherapy agents
 - Hair shafts are abruptly thinned (Pohl-Pinkus constrictions) and break off at skin surface
 - Other causes: mercury intoxication, boric acid intoxication, thallium poisoning, colchicine, severe protein deficiency
 - Histology: normal follicles
6. Trichotillomania
- Impulse-control disorder
 - Repeated plucking or pulling of hairs
 - Confluence of short sparse hairs within an otherwise normal area of the scalp
 - Varying lengths of regrowth, “friar tuck” distribution of hair loss (Fig. 1-8)
 - Regrowing hair is blunt-tipped instead of pointed
 - Eyebrows and upper eyelashes may be affected
 - Often have other habits: nail biting, skin picking
 - Histology: pigment casts, increased catagen hairs, trichomalacia
 - Treatment: psychological intervention and/or psychiatric medication to modify behavior



FIGURE 1-6 Hair mount showing a telogen hair. (Courtesy of Dr. Paradi Mirmirani.)



FIGURE 1-7 Hair mount showing a dystrophic anagen hair with a ruffled cuticle in a patient with loose anagen syndrome. (Courtesy of Dr. Paradi Mirmirani.)



FIGURE 1-8 Trichotillomania. (Courtesy of Dr. Paradi Mirmirani.)

7. Pityriasis amiantacea (Fig. 1-9)
- Thick scale, matted hair
 - May mimic severe seborrheic dermatitis or psoriasis; however, hair that is involved is easily dislodged on attempts to physically remove the scale
 - Scarring alopecia can result
 - Treatment: keratolytics, corticosteroids, oil, improves with age



FIGURE 1-9 Pityriasis amiantacea. (Courtesy of Dr. Adelaide Hebert.)



FIGURE 1-10 Traction alopecia. (Courtesy of Dr. Adelaide Hebert.)



FIGURE 1-11 Triangular alopecia. (Courtesy of Dr. Adelaide Hebert.)

8. Traction alopecia (Fig. 1-10)
 - Prolonged traction on the scalp by physical pressure: tight braids, foam rollers, tight pony tail, hair extensions
 - Hair loss may be persistent if the traction is unrelenting
9. Triangular (temporal) alopecia (Fig. 1-11)
 - Triangular patch of vellus hairs or complete hair loss-usually appears early in life
 - Frontal-temporal region
 - Histology: vellus hairs
 - No treatment, usually persistent
10. Hair loss secondary to oral contraceptives
 - Hair loss while taking oral contraceptive:
 - In women predisposed to androgenetic alopecia
 - Usually from androgenic progestins
 - Treatment: substitute oral contraceptive with less androgenic progestin
 - Hair loss after stopping oral contraceptive:
 - Onset 2 to 3 months after oral contraceptive stopped
 - May occur after stopping any of the oral contraceptives
 - Similar to postpartum effluvium, self-limited

Alopecia, Scarring

Current classification is based on histology of predominant infiltrate seen on scalp biopsy. If there is no significant infiltrate the hair loss is classified as end-stage scarring alopecia

- Predominantly lymphocytic: Pseudopelade (of Brocq), lichen planopilaris, lupus erythematosus, central centrifugal cicatricial alopecia, alopecia mucinosa

- Predominantly neutrophilic: folliculitis decalvans, dissecting cellulites
 - Mixed infiltrate: Acne keloidalis
1. Pseudopelade (of Brocq; Fig. 1-12)
 - Oval or irregularly shaped atrophic patches which may be mistaken for alopecia areata with patches of hair growth, “footprints in the snow.”
 - No scalp redness or perifollicular scale
 - Histology: atrophy, perifollicular inflammation at the level of the infundibulum, fibrosis that extends in to the subcutis
 2. Lichen planopilaris (LPP) (Fig. 1-13)
 - Perifollicular erythema and scale at the periphery of the patch of alopecia
 - > 50% associated with cutaneous or oral lichen planus



FIGURE 1-12 Pseudopelade. (Courtesy of Dr. Paradi Mirmirani.)

- Involves scalp alone or scalp and other hair-bearing areas (Graham Little syndrome)
 - Frontal fibrosing alopecia: frontotemporal hairline recession and eyebrow loss in postmenopausal women that is associated with perifollicular erythema and scaling, in a bandlike distribution along the fronto-temporal hairline
 - Histology: typically same as LPP, may see lichenoid interface dermatitis of the superficial follicular epithelium
3. Lupus erythematosus
 - Chronic cutaneous (discoid) lupus erythematosus (Fig. 1-14): scarring alopecia erythema, hypo and hyperpigmentation of the scalp, dilated follicles \pm keratin plugs, scaling at the center of the patch of alopecia
 - Systemic lupus erythematosus: diffuse, nonscarring alopecia; broken hairs in frontal region (“lupus hairs”)
 - Diagnostic biopsy and direct immunofluorescence
 - Treatment: topical, intralesional, or oral steroids; systemic retinoids; antimalarials
 4. Central centrifugal cicatricial alopecia (CCCA) (Fig. 1-15)
 - Previously called follicular degeneration syndrome; hot-comb alopecia
 - Follicular loss mainly on the crown of the scalp
 - Possibly secondary to hair care practices
 - Histology: premature desquamation of the inner root sheath, mononuclear infiltrate at the isthmus, loss of the follicular epithelium with fibrosis
 5. Alopecia mucinosa (follicular mucinosis)
 - Erythematous plaques or flat patches without hair
 - Children: head and neck, benign, self-resolving

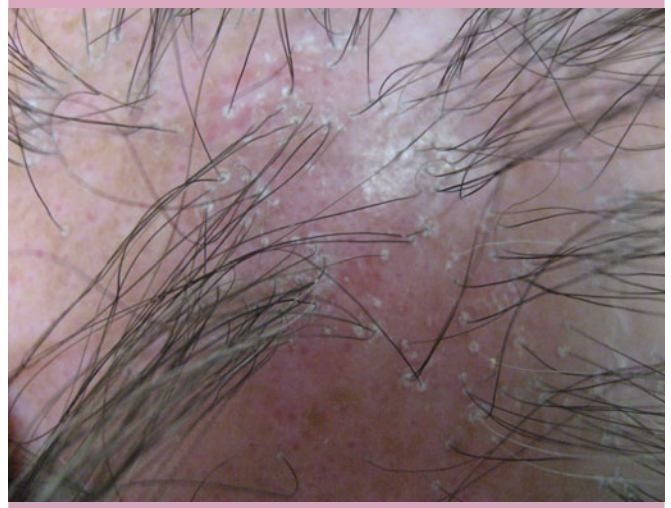


FIGURE 1-13 Lichen planopilaris. (Courtesy of Dr. Paradi Mirmirani.)



FIGURE 1-14 Discoid lupus. (Courtesy of Dr. Paradi Mirmirani.)

- Adults: more widespread distribution; may be associated with cutaneous T-cell lymphoma
 - Histology: mucin in the outer root sheath and sebaceous glands, perifollicular lymphohistiocytic infiltrate
6. Dissecting cellulitis: Perifolliculitis capitis abscedens et suffodiens (Fig. 1-16)
 - May be part of the follicular occlusion triad (cystic acne, hidradenitis, dissecting cellulitis)
 - Fluctuant nodules on vertex, occiput, sterile pus
 - Histology: sinus tracts, sterile abscesses
 - Treatment: systemic steroids, systemic antibiotics, dapsone, retinoids, surgical excision
 7. Folliculitis decalvans (Fig. 1-17)
 - Scarring alopecia with crusting, pustules and erosions
 - *Staphylococcus aureus* usually cultured



FIGURE 1-15 Central centrifugal cicatricial alopecia. (Courtesy of Dr. Paradi Mirmirani.)



FIGURE 1-16 Dissecting cellulitis. (Courtesy of Dr. Paradi Mirmirani.)



FIGURE 1-17 Folliculitis decalvans. (Courtesy of Dr. Paradi Mirmirani.)



FIGURE 1-18 Acne keloidalis. (Courtesy of Dr. Adelaide Hebert.)

- Histology: acute suppurative folliculitis with neutrophils and eosinophils; later mixed with lymphocytes and histiocytes
 - Loss of sebaceous epithelium and perifollicular fibrosis
 - Treatment: staphylococcal eradication: systemic antibiotics with or without rifampin, systemic and/or topical steroids
8. Acne keloidalis (Fig. 1-18)
 - Follicular pustules and papules that progress to firm, keloidal papules
 - Commonly on occiput of patients with coarse and/or curly hair
 - Foreign-body reaction to trapped hair shaft fragments
 - Often bacterial superinfection

- Histology: follicular dilatation and mixed periinfundibular infiltrate with follicular rupture and foreign-body granulomas
 - Treatment: systemic antibiotics, topical and/or intralesional steroids

Genetic Syndromes (Table 1-2)

 1. Anhidrotic ectodermal dysplasia (Christ-Siemens-Touraine syndrome)
- X-linked recessive form associated with defect in Ectodysplasin, pegged teeth
 - Rare autosomal dominant, autosomal recessive forms associated with defect in NEMO gene, immunodeficiency disorders
 - Thin, sparse hair
 - Absent pilosebaceous units in Blaschko’s lines
 - Hypohidrosis, atopic dermatitis, nail dystrophy

TABLE 1-2 Hair Shaft Disorders

Hair Finding	Microscopic Description	Associations
Trichorrhexis nodosa (Fig. 1-19)	Frayed nodes spaced along hair (brooms stuck end to end)	Most common hair shaft dystrophy Congenital or acquired: Arginosuccinic aciduria, Menkes’ kinky hair syndrome, citrullinemia, trichothiodystrophy Acquired disease: Proximal: common in black female hair after chemical or hot comb straightening Distal: excessive brushing
Pili trianguli et canaliculi	Hair has triangular cross section with longitudinal groove on electron microscopy	Uncombable hair syndrome
Flag sign	Intermittent reddish discoloration of hair	Kwashiorkor, anorexia nervosa
Trichorrhexis invaginata	“Bamboo hair” with intussusception of the hair shaft (ball and socket)	Netherton’s syndrome; abnormal keratinization of hair shaft in the keratogenous zone
Pili torti (Fig. 1-20)	Hair flattened and twisted from 90–360 degrees, multiple irregular intervals	Björnstad syndrome, citrullinemia, Menkes’ kinky hair syndrome, Crandall’s syndrome, Bazex’s syndrome, Salamon’s syndrome, Beare’s syndrome, trichothiodystrophy, isotretinoin therapy
Monilithrix	Elliptical nodes with a regular periodicity of 0.7–1 mm between nodes, hair shaft is constricted (fractures common)	Autosomal dominant variable expressivity; short, brittle hairs emerging from keratotic follicular papules
Pili annulati	“Zebra-striped hair” with alternating segments of light and dark color due to air cavities	Pili annulati
Trichoschisis	Clean transverse break along hair shaft where a local absence of cuticle is present	Tichothiodystrophy
Tiger tail	Zigzag alternating light and dark transverse bands on polarized microscopy	Tichothiodystrophy



FIGURE 1-19 Hair mount showing trichorrhexis nodosa. (Courtesy of Dr. Paradi Mirmirani.)



FIGURE 1-20 Hair mount showing Pili torti. (Courtesy of Dr. Paradi Mirmirani.)

- Abnormal facies: saddle nose, frontal bossing, thick lips, and peg teeth
 - Hair has longitudinal groove on electron microscopy
 - Female carriers must be watched for hyperpyrexia
2. Argininosuccinic aciduria
 - Autosomal recessive
 - Decrease in argininosuccinase
 - Most common urea cycle defect
 - Hyperammonemia, failure to thrive, hepatomegaly, seizures, ataxia, mental retardation
 - Trichorrhexis nodosa
 - Low-protein diet and arginine supplementation may reverse hair anomalies
 3. Björnstad syndrome
 - Missense mutations in the BCS1L gene on chromosome 2q34–36. Abnormal mitochondrial function, leads to the production of reactive oxygen species
 - Pili torti (spares eyelashes)
 - Bilateral sensorineural deafness correlates with the severity of hair defects
 - Crandall syndrome is pili torti and deafness with hypogonadism
 4. Hidrotic ectodermal dysplasia (Clouston's syndrome)
 - Autosomal dominant defect in gap junction protein (connexin 30)
 - Thin, sparse hair after puberty
 - Palmoplantar keratoderma, nail dystrophy, bulbous fingertips, tufted terminal phalanges
 - Normal sweating, facies, and dentition
 5. KID syndrome
 - Autosomal dominant mutation in gap junction protein GJP2 (connexin 26)
 - Keratitis (\pm blindness), ichthyosis, and deafness
 - Scarring alopecia, dystrophic nails
 6. Menkes kinky hair syndrome
 - XLR defect in MKHD gene (copper transport ATPase 7A)
 - Decreased serum copper and ceruloplasmin with increased copper in all organs *except* the liver
 - Sparse, light-colored, “steel wool” hair; pili torti (most common), trichorrhexis nodosa
 - Skin is pale with laxity and a “doughy” consistency
 - Progressive cerebral degeneration
 - Radiologic findings: wormian bones in cranial sutures, metaphyseal widening, spurs in long bones
 - Tortuous arteries, genitourinary anomalies
 7. Monilothrix
 - Autosomal dominant defect in keratins 1 and 6
 - See Table 1-2
 8. Netherton's syndrome
 - Autosomal recessive defect in *SPINK5*

- Ichthyosis linearis circumflexa, atopic dermatitis
 - Trichorrhexis invaginata (bamboo hair) is the most common hair abnormality, but trichorrhexis invaginata is the most characteristic
9. Piebaldism
 - Autosomal dominant defect in *C-KIT*
 - White forelock, depigmented patches on ventral midline
 10. Trichothiodystrophy
 - Autosomal recessive defect in *XPB/ERCC3* DNA repair transcription gene (analogous to xeroderma pigmentosum group D)
 - Ataxia but no freckling or UV-induced skin cancers
 - Trichoschisis, banding with polarized microscopy (“tiger tail”)
 - Hairs have 50% reduction in sulfur (cysteine) content
 - PIBIDS: photosensitivity, intellectual impairment, brittle hair, ichthyosis, decreased fertility and short stature
 11. Uncombable hair syndrome
 - Autosomal dominant or sporadic
 - Defect: an abnormal configuration of inner root sheath that keratinizes before the hair shaft
 - Blond, shiny, “spun glass” hair
 - Electron microscopy: pili trianguli et canaliculi, longitudinal groove, triangular shape on cross section
 - Lashes and brows are not affected
 - Biotin may help symptoms
 12. Woolly hair
 - Autosomal dominant
 - Negroid hair on the scalp of person of non-Negroid background
 - Involves only scalp hair
 - Microscopy: hair shaft tightly coiled
 - Improves with age
 13. Cronkhite-Canada syndrome
 - Sporadic
 - Extensive alopecia
 - Melanotic macules on the fingers, gastrointestinal polyposis, generalized hyperpigmentation, onychodystrophy, malabsorption/diarrhea
 14. Aplasia cutis congenita
 - Congenital absence of skin and subcutaneous tissue; may involve cranium
 - Coin-sized defect or larger
 - Often midline scalp vertex
 - Hair collar sign: ring of dark hair encircling aplasia lesion; suggests neural tube defect
 - Adams-Oliver syndrome: severe aplasia cutis congenita, cutis marmorata telangiectatica congenita, limb defects, and atrial septal defect

Infectious Disorders

1. Tinea capitis (Table 1-3; Fig. 1-21; Fig. 1-22).
 - Treatment: Griseofulvin; terbinafine, itraconazole, may add oral prednisone in case of kerion
2. Piedra
 - Gritty nodules on the hair in temperate climates
 - White piedra is caused by *Trichosporon beigelii*
 - Black piedra is caused by *Piedraia hortai*
3. Syphilis (Fig. 1-23)
 - “Moth-eaten” alopecia
4. Trichomycosis nodosa
 - Granular sheath around hair shaft
 - Axilla or pubic area
 - *Corynebacterium tenuis*, due to poor hygiene

TABLE 1-3 Presentations of Tinea Capitis

Tinea	Fungus
“Black dot” tinea: alopecia with pinpoint black dots (infected hairs that have broken off) (see Fig. 1-21)	<i>Trichophyton tonsurans</i> , <i>endothrix</i>
Kerion: boggy lesions with crust, severe inflammatory reaction (Fig. 1-22)	<i>T. mentagrophytes</i> , <i>T. verrucosum</i>
Favus: large crust of matted hyphae (scutula)	<i>T. schoenleinii</i>



FIGURE 1-21 Tinea capitis: black dot variant. (From Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill 2005, p. 709.)



FIGURE 1-22 Kerion on scalp. (Courtesy of Dr. Adelaide Hebert.)



FIGURE 1-23 Syphilis. (Courtesy of Dr. Robert Jordan.)



FIGURE 1-24 Pseudofolliculitis. (Courtesy of Dr. Robert Jordan.)

Hypertrichosis

- Overgrowth of hair not localized to androgen-dependent areas
- Local congenital or acquired hypertrichosis: melanocytic nevi, Becker's nevus (smooth muscle hamartoma), meningioma, porphyria, spinal dysraphism
- Generalized congenital hypertrichosis: X-linked dominant congenital hypertrichosis lanuginosa, fetal hydantoin syndrome, fetal alcohol syndrome
- Generalized acquired hypertrichosis: acquired hypertrichosis lanuginosa, internal malignancy, Rubenstein-Taybi, Cornelia de Lange, minoxidil, cyclosporine, phenytoin, anorexia nervosa
- Eyelash trichomegaly-HIV

Hirsutism

- Excessive terminal hair growth in androgen-dependent areas.
- Hypertrichosis is excessive hair growth in non-androgen dependent areas
- Usually related to hyperandrogenism



FIGURE 1-25 Hair mount showing bubble hair. (Courtesy of Dr. Paradi Mirmirani.)

- Polycystic ovarian syndrome: hirsutism, acne, abnormal periods, obesity
- Ovarian, adrenal, pituitary tumors
- Medications: androgens, high-progesterone oral contraceptives, minoxidil
- Treatment: waxing, plucking, shaving, bleaching, cream hair removal, electrolysis, laser, spironolactone, eflornithine cream

Miscellaneous

1. Pseudofolliculitis (Fig. 1-24)
 - Occurs at any site where hair is shaved, most common on beard
 - Ingrown hairs, foreign-body reaction
2. Green hair
 - Reaction to copper in pools
 - Treat with chelating agents
3. Bubble hair (Fig. 1-25)
 - Brittle, fragile hair from excessive heat
 - Hairdryers, straightening irons
4. Acquired progressive kinking
 - Kinking and twisting of hair shaft at irregular intervals
 - Most common in young men in frontotemporal or vertex scalp as a precursor of androgenetic alopecia
 - Rarely occurs in women or prepubertal men without progression to alopecia
 - Widespread kinking of the hair: AIDS, drugs (retinoids)

QUIZ

Questions

1. A 34-year-old Caucasian female patient complains of bothersome excess facial hair which she has been plucking for many years. She has a normal body mass index and has regular menses. On exam she has a clear complexion with terminal hair growth on the chin and neck, but no excess body hair. The most likely diagnosis is:
 - A. Hypertrichosis
 - B. Hyperandrogenism
 - C. Polycystic ovary syndrome
 - D. Hirsutism
 - E. Pseudofolliculitis
2. A 24-year-old woman is seen with gradual hair thinning over the past few years. On exam her frontal hairline is retained but the central part is widened and there are many hairs of varied length and caliber. The follicular markings are intact and there is no scaling or erythema of the scalp. A pull test is negative. A scalp biopsy will likely show:
 - A. Peribulbar lymphocytic inflammation
 - B. An increased catagen/telogen ratio
 - C. Premature desquamation of the inner root sheath
 - D. Miniaturized hair follicles with preserved sebaceous glands
3. In a normal hair follicle the inner root sheath and the hair shaft have the following relationship:
 - A. The inner root sheath is present the length of the hair shaft
 - B. The inner root sheath separates from the hair shaft at the level of the sebaceous gland
 - C. The inner root sheath is present only in pigmented hair shafts
 - D. The inner root sheath is attached to the hair shaft via strong disulfide bonds
4. A 6-year-old girl is brought in by her mother who is concerned that she has never needed a haircut. There is no family history of similar hair problems. Her daughter does not complain of any scalp itching. The blond girl has fine textured hair that covers her scalp well but is barely past her ears in length. She has no patchy or diffuse hair loss. A hair pull is done and many hairs are easily extracted. A hair mount is done. The most likely finding:
 - A. Exclamation point hairs
 - B. A telogen club hair
 - C. Dystrophic anagen hair with a ruffled cuticle
 - D. Trichorrhexis nodosa
5. Match the syndrome on the right with most common hair findings on the left:

A. Pili torti	i. Trichothiodystrophy
B. Trichorrhexis invaginata	ii. Menkes kinky hair syndrome
C. Pili trianguli et canaliculi	iii. Netherton syndrome
D. Trichoschisis	iv. Uncombable hair syndrome
E. Trichorrhexis nodosa	v. Argininosuccinic aciduria
6. The following hormone is responsible for hair miniaturization in androgen sensitive areas of the scalp:
 - A. 5-Alpha reductase type II
 - B. Testosterone
 - C. Prolactin
 - D. Dihydrotestosterone
 - E. Finasteride

7. A 60-year-old woman with previously “salt-and-pepper” hair comes in to the office complaining that her hair “turned white overnight.” Exam shows diffuse hair loss but the follicular markings are intact. There is no scaling or erythema of the scalp. A pull test is positive. A hair mount shows telogen club hairs. Your diagnosis is:
 - A. Alopecia areata
 - B. Telogen effluvium
 - C. Anagen effluvium
 - D. Androgenetic alopecia
8. A 54-year-old post-menopausal woman is seen with a complaint of a “receding hairline.” Her scalp is itchy. On exam there is a band of alopecia at the frontal hairline and extending to the temporal hairline. Where the hairline used to be, the skin is atrophic and white with loss of follicular markings. Along the current hairline there is perifollicular scaling and erythema. A scalp biopsy is done showing a dense lymphocytic infiltrate at the level of the isthmus. Your diagnosis:
 - A. Hair loss due to excess androgens
 - B. Folliculitis decalvans
 - C. Alopecia areata in an ophiasis pattern
 - D. Frontal fibrosing alopecia
9. The following is/are part of the permanent portion of the hair follicle:
 - A. Follicular melanocytes
 - B. Dermal papilla
 - C. Stem cells
 - D. All of the above
10. The following hair shaft disorders are associated with increased hair fragility and breakage:
 - i. Trichorrhexis nodosa
 - ii. Trichorrhexis invaginata
 - iii. Pili annulati
 - iv. Pili trianguli et canaliculi
 - v. Monilethrix
 - A. i and ii
 - B. all of the above
 - C. iii and iv
 - D. i, ii, v

Answers

1. D. The clinical scenario fits best with a diagnosis of idiopathic hirsutism. Hirsutism is defined as excessive terminal hair growth in androgen-dependent areas (beard, chest, axilla, pubic area). Hypertrichosis is excess hair growth in non-androgen dependent areas.
2. D. The description of hair loss fits best with a clinical diagnosis of androgenetic alopecia. The histologic findings seen in androgenetic alopecia are miniaturized follicles with retained sebaceous glands.
3. B. The inner root sheath resembles a hard mold surrounding the newly forming hair shaft. The inner root sheath moves upward with the hair shaft but separates at the level of the sebaceous gland. The inner root sheath is present in all types of hair shafts. Disulfide bonds crosslink are found in the hair cortex providing tensile strength to the hair shaft.
4. C. The clinical scenario is that of a patient with loose anagen syndrome. There is no alopecia, but the hair is somewhat sparse and fails to grow long. Hairs that are easily extracted show a hook-shaped appearance (dystrophic anagen) with a ruffled cuticle.
5. A-ii; B-iii, C-iv, D-i, E-v.
6. D. Circulating testosterone is converted to dihydrotestosterone by 5-alpha-reductase at the genetically susceptible target tissue (scalp). It is the dihydrotestosterone that is the active hormone leading to scalp hair miniaturization.
7. A. The clinical scenario describes a patient with alopecia areata. Alopecia areata not uncommonly will affect pigmented hair first, thus giving the appearance of “going white overnight.” In active alopecia areata telogen hairs or broken hairs may be seen on hair mount.
8. D. Frontal fibrosing alopecia is a primary cicatricial alopecia, lymphocytic type, thought to be a variant of lichen planopilaris. The typical patient is a post-menopausal woman with a band-like area of hair loss along the fronto-temporal rim; loss of eyebrows is variably seen. At the active border of hair loss there is perifollicular erythema and scaling.
9. C. The permanent portion of the hair follicle includes the infundibulum and isthmus. The follicular stem cells are located at the level of the bulge (insertion of the arrector pili muscle) located near the isthmus.

10. D. Hair shaft disorders are typically divided into those that cause increased fragility/breakage and those that do not. Patients with trichorrhexis nodosa, trichorrhexis invaginata, and monilethrix typically present with short, broken hair.

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EYE FINDINGS

BRENDA CHRASTIL-LATOWSKY
SYED AZHAR

EYELID ANATOMY (FIG. 2-1)

Eyelids

- Superficial to deep
 - Skin: epidermis appears atrophic, few vellus hair follicles, no subcutaneous fat
 - Obicularis oculi: Closes the eyelid, innervated by facial nerve
 - Areolar tissue: communicates with subaponeurotic layer of scalp
 - Tarsal plates: fibrous tissue responsible for structural integrity of eyelid; connected to orbital margin by lateral and medial palpebral ligaments
 - Palpebral conjunctiva: mucosal membrane
 - Sensory innervation: Terminal branches of the trigeminal nerve [cranial nerve V (CNV)]: ophthalmic (V1) and maxillary (V2) divisions

Upper Eyelid

- Extends superiorly to the eyebrow
- Upper lid retractors
 - Levator palpebrae superioris (LPS) elevates anterior portion, innervated by oculomotor nerve (CN III)
 - Müller's muscle (deeper fibers of LPS) elevates posterior portion

Lower Lid

- Extends below the inferior orbital rim to join the cheek
- Lower eyelid retractors
 - Inferior rectus is the main retractor, innervated by oculomotor nerve (CN III)
 - Inferior oblique is innervated by CNIII
 - Ptosis caused by CN III palsy and Horner's syndrome

Interpalpebral Fissure

- Fusiform space between the eyelid margins (usually 10–11 mm in youth; decreases with age to 8–10 mm)

Eyelashes

- Lid margins have horizontal row of irregularly-arranged eye lashes anteriorly and approximately 25 openings of Meibomian glands posteriorly
- More eyelashes on top lid margin
- Trichiasis
 - Misdirected eyelashes that rub on the cornea
 - Very common acquired condition
 - Results in ocular irritation made worse on blinking
 - Caused by chronic blepharitis, herpes zoster ophthalmicus (see below), trauma, or chemical injuries to eyes
- Distichiasis
 - Eyelashes grow abnormally from meibomian gland openings, resulting in 2nd row of eyelashes
 - Results from intense inflammation of eyelids, such as from cicatricial pemphigoid or Stevens-Johnson syndrome, or may be congenital (see below)
- Lymphedema-Distichiasis syndrome
 - Autosomal dominant with high penetrance, variable expressivity
 - Mutation in the FOXC2 gene, a transcription regulator
 - Epithelial germ cells destined to develop into Meibomian glands instead differentiate into complete pilosebaceous units
 - Second row of posteriorly-directed eyelashes
 - Lymphedema of the legs
- Trichomegaly (Table 2-1)
- Entropion
 - Inward turning of the eyelid margin from infection, scarring, mechanical trauma
 - Causes irritation, redness, and stringy white mucoid discharge
- Ectropion
 - Outward turning of the eyelid margin from lower eyelid laxity, mechanical (collodion membrane)

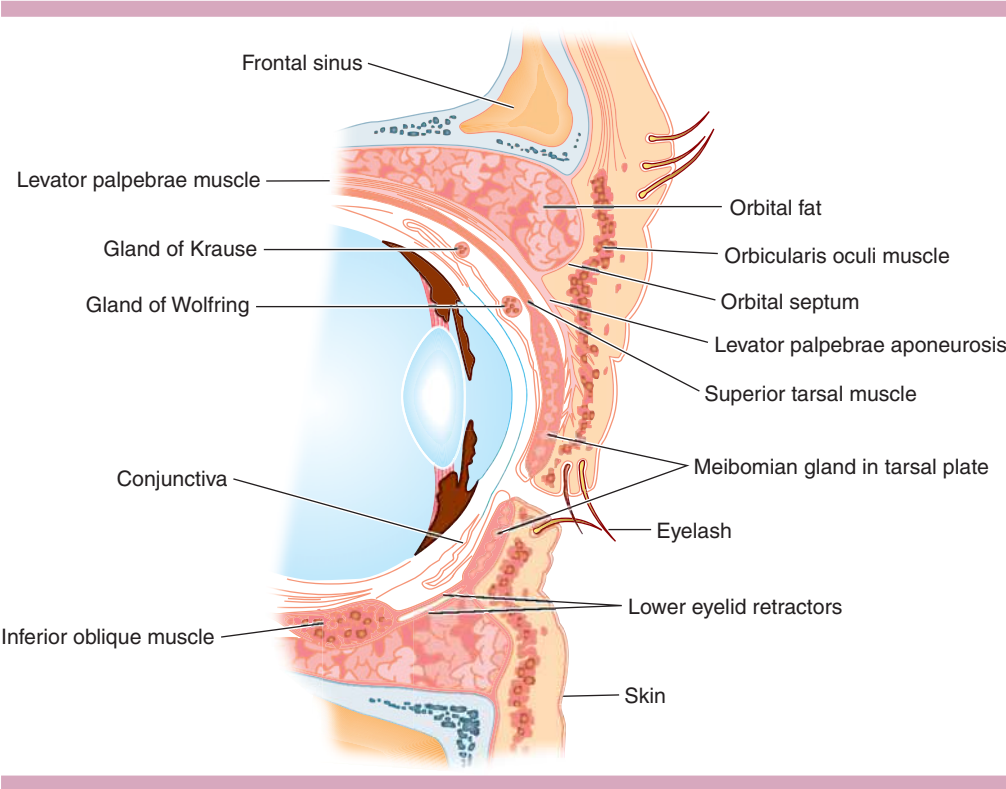


FIGURE 2-1 Eyelid anatomy. (Redrawn with permission from Riordan-Eva P, Richter JP: *Vaughan & Ashbury’s General Ophthalmology*, 17th Ed. New York: McGraw-Hill; 2008.)

TABLE 2-1 Causes of Trichomegaly

Acquired
Drug-induced: phenytoin, cyclosporine, topical prostaglandin analogues, interferon α 2a, epidermal growth factor inhibitors, systemic tacrolimus
Malnutrition
Acquired immunodeficiency syndrome (AIDS)
Porphyria
Hypothyroidism
Familial
Congenital
Cornelia de Lange syndrome: synophrys, low hairline, developmental and musculoskeletal abnormalities
Hermansky-Pudlak syndrome: albinism and bleeding diathesis
Oculocutaneous albinism type I
Oliver-MacFarlane syndrome: retinitis pigmentosa, short stature (GH deficiency), trichomegaly, and hair anomalies
Adapted from Kanski JJ: <i>Clinical Ophthalmology: A Systematic Approach</i> , 6th Ed. Burlington, Massachusetts: Butterworth-Heinemann; 2007, Table 4.1.

- Causes tearing, corneal irritation and conjunctival redness, dry eyes
- Lower eyelid is involved most commonly
- Dermatochalasis (Fig. 2-2)
 - Redundant eyelid skin and fat
 - May result in functional loss of superior vision if the tissue hangs over the eyelid margin
- Blepharoptosis (Fig. 2-3)
 - Drooping of the margin of the eyelid, may cause functional vision loss
 - Etiology includes age-related dehiscence of the levator muscle, Horner's syndrome, third cranial nerve palsy, myasthenia gravis, and trauma



FIGURE 2-2 Dermatochalasis of upper lids and herniation of orbital fat of lower lids. (Reproduced with permission from Riordan-Eva P, Richter JP: Vaughan & Ashbury's General Ophthalmology, 17th Ed. New York: McGraw-Hill; 2008.)



FIGURE 2-3 Blepharoptosis. (Reproduced with permission from Riordan-Eva P, Richter JP: Vaughan & Ashbury's General Ophthalmology, 17th Ed. New York: McGraw-Hill; 2008.)

Glands of the Eyelid

- Zeis glands
 - Small, modified sebaceous glands
 - Open into the hair follicles at the base of the eyelashes
 - External hordeolum (stye): Staph infection of lash follicle and associated gland of Zeis
- Meibomian glands
 - Sebaceous glands, present within the tarsus; secrete lipid layer of tear film
 - Chalazion (Meibomian cyst) (Fig. 2-4): granulomatous reaction to sebaceous secretion into surrounding stroma
 - Nontender, firm nodule located deeply within the tarsal plate about 5 mm from the lid margins
 - Eversion of the lid may reveal the inflamed meibomian gland
 - Internal hordeolum: chalazion superinfected with Staph
 - Both internal and external hordeolum can arise as a secondary complication of blepharitis
- Glands of Moll
 - Apocrine glands
 - Located anterior to the meibomian glands within the distal eyelid margin
 - Apocrine hidrocystoma (cyst of Moll) – translucent, bluish cyst on anterior margin of eyelid. Eccrine hidrocystoma usually located medially or laterally and does not involve the lid margin
 - Schopf-Schulz-Passarge syndrome
 - Autosomal recessive
 - Hidrocystomas of eyelids
 - Hypotrichosis, hypodontia, nail abnormalities
 - Palmarplantar eccrine syringofibroadenosis

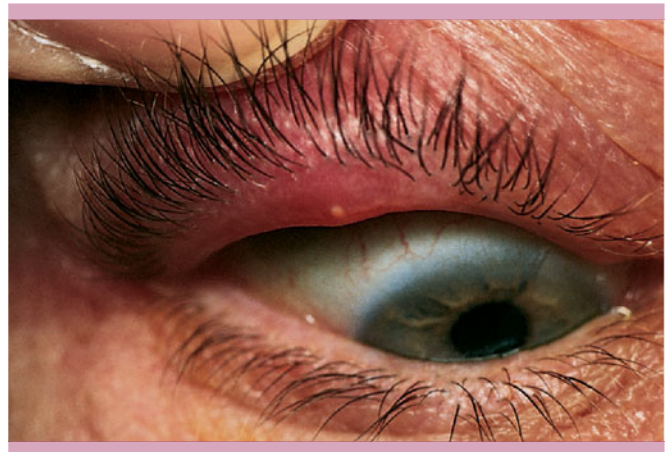


FIGURE 2-4 Chalazion. (Reproduced with permission from Knoop K: Atlas of Emergency Medicine. New York: McGraw-Hill; 2002.)

CONGENITAL ABNORMALITIES

Albinism (See Chapter 29)

- Oculocutaneous albinism
 - Involves both the skin and eyes
- Ocular albinism
 - Mainly affects the eyes with minimal to no skin involvement
 - Sex-linked or autosomal recessive disease: reduction in the number of melanosomes
- Color of the iris usually is blue for tyrosinase-negative albinism, blue to yellow-brown for tyrosinase-positive albinism

Ataxia-Telangiectasia (Louis-Bar Syndrome) (Fig. 2-5) (See Chapter 32)

- Autosomal recessive, defect in *ATM* gene on 11q22-23
- Telangiectasia of the bulbar conjunctiva (first appears at 3–5 years)
- Accelerated aging of skin and vessel changes on eyelids (rare)
- Strabismus and nystagmus
- Poor ability to initiate rapid eye movements
- Visual acuity, pupillary reflex responses, and fundi are normal

Juvenile Xanthogranuloma (JXG)

- Non-Langerhans cell histiocytosis with Touton giant cells (under age 2 years)
- Ocular involvement is the most common extracutaneous site
- Orbital masses, unilateral glaucoma, yellowish brown iris lesions resulting in iris heterochromia and spontaneous hyphema, uveitis
- JXG in a patient with neurofibromatosis type 1 signals a 20-fold to 32-fold increased risk for juvenile chronic myelogenous leukemia



FIGURE 2-5 Ataxia-telangiectasia. (From Paller AS: *Hereditary immunodeficiency disorders*, in Alper JC, ed. *Genetic Disorders of the Skin*. Chicago: Mosby Year Book; 1991, p. 105.)

Nevus of Ota (Ocular Melanocytosis or Melanosis Oculi) (See Fig. 8-2)

- Unilateral congenital pigmented lesion of sclera (bluish or slate gray)
- May involve eyelid or adjacent skin with dermal hyperplasia (commonly seen in Asians)
- Higher incidence of glaucoma and possibly malignant melanoma

Down's Syndrome (See Chapter 32)

- Trisomy 21
- Brushfield's spots (white spots indicative of hyperplasia of iris) present in 90% of patients
- Prominent epicanthal folds
- Amblyopia
- High refractive errors
- Glaucoma during infancy
- Cataracts, early or late

Cockayne's Syndrome (CS) (See Chapter 32)

- Autosomal recessive
- CS type 1 is caused by a defect in the Cockayne syndrome type A gene (*CSA* or *ERCC8*) located on chromosome 5
- Mutations in the DNA excision repair gene *ERCC6* located on band 10q11 cause CS type 2
- In some patients there is an overlap with xeroderma pigmentosa complementation group B, D or G
- Retinitis pigmentosa ("salt and pepper retina")
- Cataracts in children younger than 3 years
- Optic atrophy or optic disk pallor

Gardner Syndrome (Familial Adenomatous Polyposis) (See Chapter 32)

- Autosomal dominant
- Mutations in the tumor suppressor adenomatous polyposis coli gene (*APC*) on 5q21-22
- Mutations on the *APC* gene that correlate with congenital hypertrophy of the retinal pigment epithelium (CHRPE) are between codon 311 on exon 9 and codon 1444 on exon 15
- Benign hyperpigmented lesion of the retinal pigment epithelium
- Typically smaller, multiple, and bilateral in Gardner syndrome (50–80%)

Hypomelanosis of Ito (Incontinentia Pigmenti Achromians)

- Mosaicism of the X chromosome
- Retinal pigment abnormalities: radial hypopigmented streaks
- Unilateral heterochromic iris

- Hypopigmentation of the cornea, strabismus, and hypertelorism
- Cataracts and retinal detachment

Epidermal Nevus Syndrome (See Chapter 11)

- Mosaicism
- Epidermal nevi, which may involve eyelid and bulbar conjunctiva
- Lipodermoid tumors
- Coloboma
- Corneal opacities

Incontinentia Pigmenti (Bloch-Sulzberger Syndrome) (See Chapter 8)

- X-linked dominant defect in NEMO
- Retina with mottled, diffuse hypopigmentation (nearly pathognomonic)
- Abnormal peripheral retinal vessels with areas of nonperfusion (very common), retrolental membrane formation (pseudoglioma), cataracts, glaucoma, microphthalmos, nystagmus, and strabismus
- Optic atrophy or foveal hypoplasia
- 1/3 of children have retinal detachment in the first year of life, resulting in white pupillary reflex (leukocoria)

Leopard Syndrome (Moynahan Syndrome)

- Autosomal dominant
- Defect in *PTPN11*, encoding the tyrosine phosphatase SHP-2 located on 12q24.1
- Mutation results in loss-of-function
- Lentigines (spares the mucous membranes), electrocardiographic (ECG) conduction defects, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, deafness

Nail Patella Syndrome (See Chapter 11)

- Also known as hereditary osteonychodysplasia (HOOD)
- Autosomal dominant
- Defect in transcription factor gene *LMX1B*
- Lester iris: hyperpigmentation of the pupillary margin of the iris (45% of patients)
- Heterochromia of the iris with cloverleaf deformity, cataracts, microcornea, and glaucoma

Xeroderma Pigmentosum (See Chapter 32)

- Autosomal recessive
- Progressive photophobia, conjunctivitis, pigmentation of eyelids and conjunctivae
- Ectropion
- Benign lid papillomas and malignant tumors: BCC, SCC, melanoma

Goldenhar Syndrome (Oculo-Auriculo-Vertebral Dysplasia)

- Sporadic
- Upper lid coloboma
- Microphthalmos (presence indicates increased risk of mental retardation)
- Epibulbar tumors
- Microtia
- Preauricular acrochordons
- Hypoplasia of malar, maxillary and mandibular regions
- Macrostomia

Treacher Collins Syndrome

- Defect in first and second branchial arch structures
- Autosomal dominant
- Lower lid coloboma (77%)
- Downward slanting of the palpebral fissures (antimongoloid)
- Cataracts
- Normal intelligence in most
- Malformation of the pinnae and conductive hearing loss
- Hypoplastic mid-face: bilateral and symmetric mandibular and zygomatic hypoplasia
- Micrognathia

Apert Syndrome (Alpert's Syndrome)

- Premature fusion of all cranial sutures
- Autosomal dominant and sporadic (associated with increased paternal age)
- Major criteria: craniosynostosis and syndactyly
- Flattened occiput and prominent forehead
- Mid-facial hypoplasia and beaked nose
- Acneiform eruption of trunk and extremities, moderate-severe acne at adolescence in 70%
- Downward slanting palpebral fissures
- Amblyopia and strabismus

Crouzon Syndrome

- Autosomal dominant
- Most common mutation: *FGFR2* on chromosome 10
- Mutation in the *FGFR3* gene associated with acanthosis nigricans
- Hypoplastic midface
- Mandibular prognathism
- Proptosis secondary to shallow orbits
- Hypertelorism
- Blue sclerae reported less commonly

Riley-Day Syndrome (Familial Dysautonomia)

- Autosomal recessive
- Hyperhidrosis
- Generalized lack of response to pain
- Lack of tears

- Decreased corneal sensation
- Miosis of the pupil in response to 2.5% methacholine (no response in normal subjects)

CONNECTIVE TISSUE DISORDERS

Ehlers-Danlos Syndrome (See Chapter 32)

- Abnormalities in the synthesis and metabolism of collagen
- Most ocular abnormalities occur in the kyphoscoliosis type (previously known as type VI)
- Autosomal recessive
- Mutations in the *PLOD* gene
- Defect in lysyl hydroxylase
- Retinal detachments, microcornea, myopia, blue sclera, angioid streaks, keratoconus, myopia, lens subluxation, and ocular fragility can lead to a ruptured globe/blindness

Marfan's Syndrome (See Chapter 32)

- Autosomal dominant
- Defect mutations in the fibrillin-1 (*FBN1*) gene located on chromosome 15q21.1
- Fibrillin needed to form microfibrils
- Structural component of the suspensory ligament of the lens
- Lens subluxation (50–80%)
 - Lense tends to displace superotemporally
 - Typically present at birth and is nonprogressive
 - Can result in hyperopic or myopic shift, astigmatism
- Slit-lamp exam
 - Displaced crystalline lens
 - Appears as a black crescent at the edge of the lens against a red reflex from the fundus
- Other ocular anomalies
 - Flat cornea
 - Increased axial length of the globe resulting in myopia (nearsightedness) and retinal detachment
 - Glaucoma and cataracts in patients younger than 50 years
 - Hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis

Osteogenesis Imperfecta (Table 2-2) (See Chapter 32)

- Autosomal dominant
- Blue sclera is caused by thinness and transparency of the collagen fibers of the sclera allowing visualization of underlying uvea
- Also may present with keratoconus, megalocornea, anterior embryotoxon, congenital glaucoma, zonular cataract, dislocated lens, choroidal sclerosis, retinal hemorrhage

Pseudoxanthoma Elasticum (PXE) (See Chapter 32)

- Autosomal recessive

TABLE 2-2 Ocular Findings in Osteogenesis Imperfecta

Type	Ocular Finding
I	Premature arcus senilis, blue sclera
II	Dark-blue sclera
III	Sclera of variable hue
IV	Normal sclera

- Defect in *ABCC6* gene
- Cutaneous and ocular findings of PXE are referred to as Grönblad-Strandberg syndrome
- Increased amounts of elastic tissue that become calcified
- Angioid streaks
 - Dark-red to brown bands that are breaks in the thickened and calcified Bruch membrane
 - Radiate from the optic nerve
 - Bruch's membrane is a collagen- and elastin-containing membrane between the retina and the choroid
- Macular degeneration, retinal hemorrhage, choroidal ruptures

Waardenburg Syndrome (Table 2-3) (See Chapter 29)

- Autosomal dominant
- Defect of neural crest cell migration and differentiation
- Dystopia canthorum (most common)
- Distance between the inner angles of the eyelids is accompanied by increased distance between the inferior lacrimal points
- Heterochromic irides, bilateral isohypochromia iridis (pale-blue eyes)
- Strabismus
- Albinotic fundi: generalized decrease in retinal pigment

Werner Syndrome (Progeria Adulorum) (See Chapter 32)

- Autosomal recessive
- Defect in the *WRN* gene (DNA helicase)
- Posterior subcapsular cataracts (20–40 years)

Focal Dermal Hypoplasia (Goltz Syndrome) (See Chapter 32)

- X-linked dominant, Xp22
- Heterochromia, irregularity of the pupils, aniridia, lens subluxation
- Colobomas of the iris, choroid, retina, or optic disc
- Corneal defects, cloudiness of the vitreous, widely spaced eyes

TABLE 2-3 Waardenburg Syndrome: Defects and Associations

Type	Defect	Associations
I	<i>PAX3</i>	Dystopia canthorum, convergent strabismus (blepharophimosis), and reduced visibility of the medial sclera
II	<i>MITF</i>	Heterochromia iridium, no dystopia canthorum
III	<i>PAX3</i>	Dystopia canthorum
IV	<i>SOX10</i>	Hirschsprung's disease

- Microphthalmia, anophthalmia, optic nerve hypoplasia
- Ectropion, ptosis, nystagmus, photophobia, strabismus

Lipoid Proteinosis (Urbach-Wiethe Disease) (See Chapter 27)

- Autosomal recessive
- Mutation in extracellular matrix protein 1
- Eyelid “string of pearls”

Naegeli-Franceschetti-Jadassohn Syndrome

- Rare autosomal dominant form of ectodermal dysplasia
- Hypohidrosis and palmarplantar keratoderma
- Lack of dermatoglyphics
- Dermatoocular syndrome (starting at age 2)
- Reticular pigmentation of the neck, chest, and abdomen, improving with age
- Spotlike pigmentation may be present around the mouth and eyes

Hay-Wells Syndrome

- Ankyloblepharon-ectodermal dysplasia-clefting (AEC) syndrome
- Autosomal dominant
- Sparse eyelashes
- Cleft palate and cleft lip
- Ankyloblepharon filiforme adnatum

CHANDS Syndrome

- Autosomal recessive with pseudodominance
- Curly hair
- Ankyloblepharon
- Nail Dysplasia (hypoplastic nails)

KERATOTIC DISEASES (TABLE 2-4)

CHIME Syndrome

- Colobomas of the eye, heart defects, ichthyosiform dermatosis, mental retardation, and ear defects

Vogt-Koyanagi-Harada Syndrome (See Chapter 29)

- Pathogenesis targets melanocytes
- HLA-DR1 and 4
- Granulomatous uveitis/iridocyclitis, swollen optic disc, chorioiditis, vitreous opacities, and serous retinal detachments
- The above findings are followed several weeks later by poliosis of eyelashes and brows and vitiligo, depigmented fundus and limbic lesions

VASCULAR DISORDERS

Osler-Weber-Rendu (Hereditary Hemorrhagic Telangiectasia) Syndrome (See Chapter 32)

- Autosomal dominant
- Defects in endoglin and activin receptor-like kinase type I (*ALK-1*) genes, which encode for TGF- β receptor
- Conjunctival telangiectasias by 3 to 6 years of age

Capillary Hemangiomas

- One of the most common benign orbital tumors of infancy (females 2:1)
- Benign endothelial cell and vascular channel neoplasms that are typically absent at birth and characteristically have rapid growth in infancy
- Ocular morbidity related to space-occupying effects
- Amblyopia (43–60%), astigmatism, strabismus with eyelid involvement
- Presentation: unilateral, superonasal, eyelid, or brow lesion

Sturge-Weber Syndrome

- Disease characterized by facial capillary malformation with underlying soft tissue and skeletal hypertrophy, ipsilateral arteriovenous (AV) malformation, cerebral calcification, hemiparesis, hemianopia, contralateral seizures, and some mental deficiency
- Glaucomas: 60% at birth or early infancy and 30% presenting during childhood, almost always unilateral and ipsilateral to the port-wine stain
- “Tomato catsup” fundus with a bright-red or red-orange color
- Tortuous conjunctival and episcleral vascular plexuses
- Choroidal angiomas (indirect binocular ophthalmoscopy)
- Anisometropic amblyopia

TABLE 2-4 Keratotic Diseases: Inheritance, Gene Defects and Ocular Findings

Disorder	Inheritance	Enzyme defect	Ocular Findings
X-linked ichthyosis	X-linked recessive	Steroid sulfatase	Comma-shaped corneal deposits
Lamellar ichthyosis	Autosomal recessive	Transglutaminase 1	Ectropion, megalocornea
Refsum syndrome	Autosomal recessive	Phytanic acid oxidase deficiency	“Salt-and-pepper retina,” cataracts, nystagmus, night blindness
Sjögren-Larsson syndrome	Autosomal recessive	Fatty alcohol oxidoreductase deficiency	“Glistening dots,” pigmentary retinopathy
Conradi-Hunermann syndrome	X-linked dominant	<i>PEX7/EBP</i>	Asymmetric focal cataracts, optic nerve hypoplasia
KID (keratitis, ichthyosis, deafness) syndrome	Autosomal dominant and autosomal recessive reported	<i>GJP2/Connexin26</i>	Keratitis, blindness, photophobia

TUMORS

Basal Cell Carcinoma (BCC) (Fig. 2-6)

- Most common epithelial tumor of the eyelid
- Most common location is the lower eyelid (48.9–72.1%)
- Highest recurrence in lesions arising from the medial canthus (60%)
- Nodular BCC most common type

Squamous Cell Carcinoma (SCC) (Fig. 2-7)

- Approximately 5% of malignant eyelid tumors
- Incidence of metastasis is 0.23–2.4% of cases
- Location of lesion most common on lower eyelid, then lid margin

Sebaceous Cell Carcinoma

- Female predilection
- May mimic either a chalazion or chronic blepharitis
- Invades locally and can spread to regional lymph nodes
- It arises generally from the meibomian glands and glands of Zeis
- Predilection for the upper lid
- Yellowish, firm, painless, indurated papule or ulceration
- May arise from meibomian glands (most common), Zeis glands, or glands associated with the caruncle
- Large anaplastic cells with open vesicular nuclei and prominent nuclei set in foamy or frothy cytoplasm, pagetoid spread
- Overall mortality rate 5–10%
- Associated with Muir-Torre syndrome

Nevus (Fig. 2-8)

- Nevi are well-demarcated, flat or elevated, pigmented or nonpigmented lesions

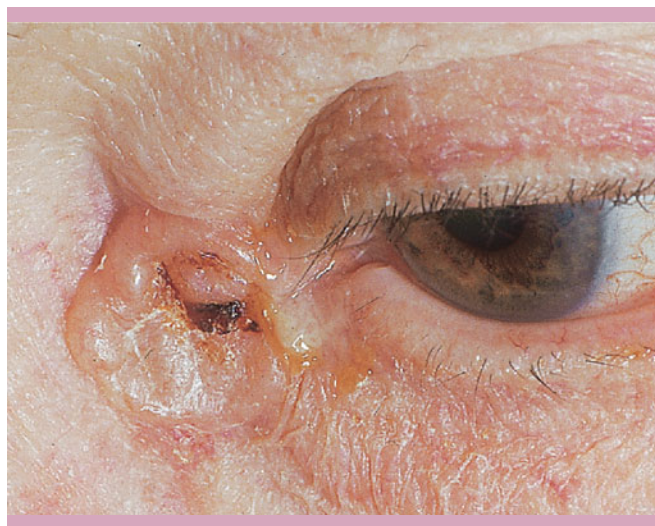


FIGURE 2-6 Basal cell carcinoma in “danger” zone A. Smooth, glistening, pearly tumor with telangiectasia. Basal cell carcinomas arising in the central area of the face, in the nasolabial folds, around the eye, and in the sulcus behind the ear (“danger zones”) must be removed with Moh’s surgery to prevent unmanageable recurrences, as these tumors move deeply along the fascial planes. (Reproduced with permission from Wolff K et al. *Fitzpatrick’s Color Atlas and Synopsis of Clinical Dermatology*, 5th Ed. New York: McGraw-Hill; 2005.)

- May become more pigmented, more elevated, or cystic during adolescence or young adulthood
- Pigmented lesions that have changed in appearance should be excised



FIGURE 2-7 Squamous cell carcinoma. (From Lowenstein J, Lee S: *Ophthalmology: Just the Facts*. New York: McGraw-Hill; 2004, p. 76.)



FIGURE 2-8 Nevus. (From Lowenstein J, Lee S: *Ophthalmology: Just the Facts*. New York: McGraw-Hill; 2004, p. 92.)

Melanoma (Fig. 2-9)

- Rare pigmented eyelid tumor
- Must be differentiated from nevi and BCC
- Change in the appearance of a pigmented lesion warrants excisional biopsy of the lesion

Merkel Cell Carcinoma (Fig. 2-10)

- Rarely suspected clinically
- 2/3 of all patients with Merkel cell carcinoma have lymph node metastases within 18 months of diagnosis, 1/3 develop hematogenous spread
- Affects the elderly
- Upper eyelid most commonly affected
- Violaceous, well demarcated nodule with little epidermal change



FIGURE 2-9 Melanoma. (From Lowenstein J, Lee S: *Ophthalmology: Just the Facts*. New York: McGraw-Hill; 2004, p. 96.)

SYSTEMIC HAMARATOMA SYNDROMES

Tuberous Sclerosis (See Chapter 32)

- Autosomal dominant and spontaneous mutations (66%)
- Hamartin and tuberlin found on chromosomes 9 and 16, respectively
- Hypopigmented macule in the iris, seizures
- Retinal hamartomas (phakomas), astrocytic hamartomas: whitish gray nodular lumps with a mulberry appearance, glial cell in origin and may calcify, some lesions are flat and smooth
- Retinal hamartomas are usually benign, but there are reports of aggressive growth, resulting in retinal detachment and glaucoma (some cases have required enucleation of the eye)
- Nystagmus and angioid streaks

Neurofibromatosis I (See Chapter 32)

- Autosomal dominant, nearly half are sporadic
- *NF-1* encodes Neurofibromin, and is found on 17q11.2
- Congenital glaucoma
- Lisch nodules (iris hamartomas) (Fig. 2-11), tan, asymptomatic nodules that develop in the first to third decades (usually before 6 years of age)
 - Present in 95% of patients
 - Found on slit-lamp examination
- Optic nerve glioma occurs in 15% and may involve other brain structures
- Plexiform neurofibroma of the orbit or eyelid leading to glaucoma and ptosis, ectropion uveae, retinal hamartoma, prominent corneal nerves
- Choroidal nevi
 - May have increased risk of developing into melanoma

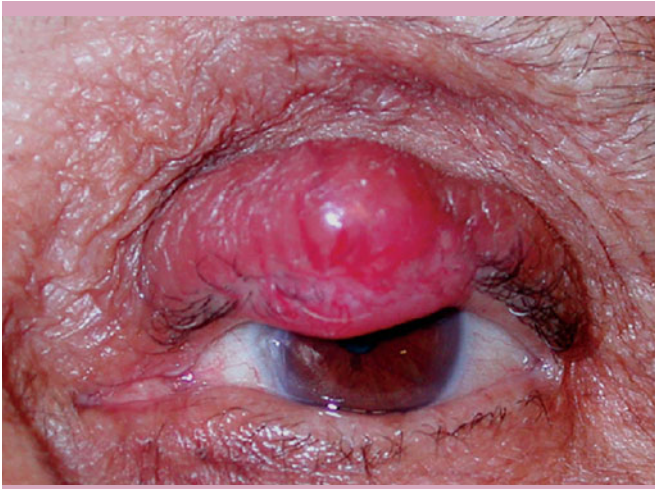


FIGURE 2-10 Merkel cell carcinoma on the eyelid arising 3 months before biopsy. The lesion was initially presumed to be a chalazion or cyst. (Reproduced with permission from Wolff K et al. *Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- Spheno-orbital encephalocele causes a pulsating proptosis and results from sphenoid wing dysplasia
 - Bruit or thrill may be present

Neurofibromatosis II (See Chapter 32)

- Autosomal dominant, rare melanocytic and cutaneous lesions
- *Schwannomin* gene codes for Merlin on chromosome 22
- Bilateral acoustic neuromas usually present in second to third decades
- Meningiomas, schwannomas, and ependymomas
- Juvenile posterior subcapsular cataract (2/3 of patients)
- 10% have ocular motor defects

von-Hippel-Lindau Syndrome (See Chapter 32)

- Autosomal dominant inheritance with variable penetrance
- *VHL* gene on chromosome 3
- Congenital hemangioblastomas of retina (50% of patients) and optic nerve
- In patients with retinal angiomas, 25% have associated cerebellar hemangioblastomas
- Serum leakage from these vessels
- Visual complications of retinal angiomas include macular exudation, retinal detachment, vitreous hemorrhage, cataract, glaucoma, and nerve damage
- Angiomas have a poor prognosis unless they are treated
- Treatment: argon laser photocoagulation, cryotherapy, or irradiation, fluid drainage, scleral buckling, penetrating diathermy, vitreous surgery



FIGURE 2-11 Lisch nodules. (From Freedberg IM et al. *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003, p. 1828.)

COLLAGEN-VASCULAR DISEASES

Sjögren Syndrome (See Chapter 25)

- Autoimmune condition (SSA (Ro) and SSB (La) antigens) of lacrimal and salivary glands
- Human leukocyte antigen B8 (HLA-B8), DR3, DQw2 and DRw52 antigens
- Xerophthalmia: foreign body sensation is an early sign
- Repeated blinking and rubbing results in minor corneal abrasions, which may produce photophobia
- Keratoconjunctivitis sicca, punctate keratopathy, uveitis, optic neuritis, scleritis
- Rarely, Adie pupil (tonic pupil) – response to light and accommodation is sluggish
- One of the few conditions to produce bilateral enlargement of lacrimal (and salivary) glands
 - Rapid enlargement, however, warrants a workup for B-cell lymphoma

Relapsing Polychondritis (RP)

- Episodic inflammatory condition involving cartilaginous structures
- Antibodies to collagen type II
- HLA-DR4
- Inflammation of almost every part of the eye: conjunctivitis, episcleritis, scleritis, uveitis, retinopathy, diplopia, and eyelid swelling

Polyarteritis Nodosa (PAN)

- Disease with necrotizing inflammation of medium- or small-sized arteries
- Hypertensive and ischemic retinopathy, central nervous system (CNS) lesions resulting in visual loss,

CN palsies, scleritis, marginal corneal ulceration, interstitial keratitis, occlusive retinal periarteritis

Dermatomyositis (DM) (See Chapter 25)

- Heliotrope rash: violaceous to dusky erythematous rash, most prominent on upper eyelids
- With or without edema in a symmetric distribution involving the periorbital skin
- Rare ophthalmoplegia owing to myositis of extraocular muscles
- Retinopathy may occur in juvenile dermatomyositis

Wegener Granulomatosis (WG)

- Autoimmune inflammatory process with necrotizing granulomas
- Antineutrophil cytoplasmic antibodies (c-ANCA) directed at neutrophil proteinase 3 (PR-3)
- Ocular involvement in 29–58%; can be localized to the orbit
- Orbital pseudotumors causing refractile proptosis, pain and loss of vision
- Nasolacrimal duct stenosis
- Uveitis
- Nodular scleritis, peripheral keratitis, and retinal vasculitis

Sarcoidosis (Fig. 2-12) (See Chapter 30)

- Multisystem granulomatous disease of unknown etiology; ocular or lacrimal involvement in 25%
- Lacrimal gland and ductal involvement
- Conjunctival granulomatous nodules
- Interstitial keratitis
- Cataract and glaucoma: complication of uveitis and/or the corticosteroid treatment
- Anterior uveitis: most common ocular manifestation of sarcoidosis with mutton fat keratic precipitates, iris nodules (Busacca and Koeppe), iris synechiae
- Glaucoma: both open-angle and angle-closure
- Retinal neovascularization, periphlebitis, perivascular cuffing and exudates
- Vitreous cavity inflammation (pars planitis), chorioidal lesions
- Rarely neurosarcoid: granulomas of the optic nerve (CN II) along with oculomotor nerves (CNs III, IV, and VI)
- May cause diplopia, ptosis, or paresis of extraocular muscles
- Heerfordt syndrome (uveoparotid fever)
 - Fever, uveitis, which may precede the parotid enlargement, and facial nerve palsy
- Löfgren syndrome
 - Fever, erythema nodosum, bilateral hilar adenopathy, and arthralgias
 - Associated with anterior uveitis in 6% of patients
- Mikulicz syndrome

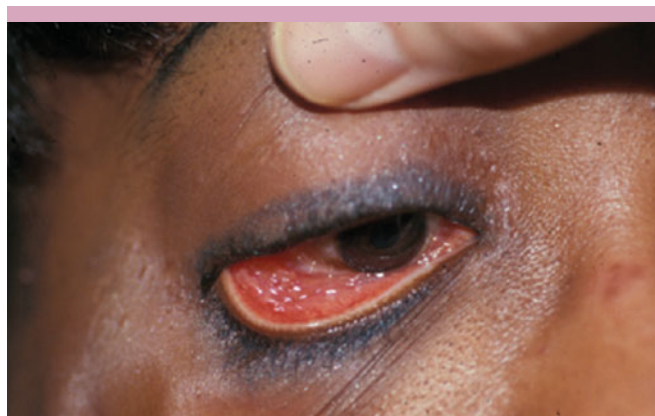


FIGURE 2-12 Sarcoidosis. (Courtesy of Dr. Steven Mays.)

- Parotid, submandibular, sublingual and lacrimal glands affected

BULLOUS DERMATOSES

Ocular Cicatricial Pemphigoid (OCP) (See Chapter 10)

- Autoantibodies directed against
 - Bullous pemphigoid antigen 2 at a site near the lamina densa (explains the scarring)
 - Autoantibodies bind the epidermal side of salt-split skin
 - β_4 subunit of $\alpha_6\beta_4$ -integrin (205-kDa protein, also known as CD104)
 - Epiligrin (laminin 5, α subunit) ligand for $\alpha_6\beta_4$ -integrin
 - Autoantibodies bind to the dermal side of salt-split skin
 - Autoantibodies cross-react with the alpha subunit of laminin-6
- Mouth most common site affected in cicatricial pemphigoid
- Ocular anomalies in older individuals (70 years mean age)
- Ocular involvement more common in patients with oral involvement (75%) versus skin without oral involvement (25%)
- Involvement is bilateral, but disease may initially present unilaterally; signs and symptoms may be asymmetrical
- Early disease is subtle: irritation, dry eye, discharge
 - Can detect disease involvement by slit-lamp exam
- Chronic conjunctivitis may lead to scarring, blindness if untreated
- Scarring leads to conjunctival shrinkage, symblepharon, fibrotic bands, trichiasis

- Differential diagnosis includes cicatrizing conjunctivitis resulting from use of pilocarpine, guanethidine, ephedrine or idoxuridine
- There are reports of ocular cicatricial pemphigoid that began after severe ocular injury resulting from Stevens-Johnson syndrome

Stevens-Johnson Syndrome

- Delayed hypersensitivity reaction to drugs, usually acute (HLA-B12, –A29, DR7)
- Other causes: infection, vaccination, systemic diseases, physical agents
- Incidence in HIV patients is 3 times higher than that of the general population
- Conjunctivitis, chemosis, vesicles, bullae, membranes, ulceration
- Bilateral lacrimation
- Swollen and ulcerated eyelids leading to entropion, dry eyes
- Subepithelial fibrosis, lagophthalmos, corneal ulceration, vascularization, opacification, and rarely, perforation
- Scarring manifests as conjunctival shrinkage, foreshortening of fornices resulting in symblepharon ankyloblepharon, trichiasis

METABOLIC DISORDERS (TABLE 2-5)

Alkaptonuria (Fig. 2-13) (See Chapters 11, 27)

- Autosomal recessive
- Deficiency of homogentisic acid oxidase, encoded on chromosome 3
- Causes ochronosis

- Incidence higher in Slovakian population
- Bluish black discoloration of sclerae
- Osler sign: blue-black pigment in sclera near insertion of rectus muscles
 - Usually triangular, with base facing site of muscle insertion
 - First ocular manifestation to appear
- Oil-droplet opacities in cornea
- Pigmented pinguecula in the shape of rings

Fabry Disease (See Chapters 9, 27)

- X-linked recessive
- Defect in α -galactosidase
- Characteristic corneal opacities: cornea verticillata (whorled corneal deposits)
 - Amiodarone and chloroquine produce deposits that appear identical
- “Fabry cataract”: spokelike lens deposits of posterior lens
 - Unique to Fabry’s and found in males and female carriers
 - First ocular manifestation
- Conjunctival and retinal vascular lesions: early in life there is tortuosity, aneurysms of venules and sausage-like dilation of veins
 - Later, systemic hypertension produces retinal changes
- Oculomotor abnormalities

Hepatolenticular Degeneration (Wilson Disease) (Fig. 2-14) (See Chapter 27)

- Autosomal recessive
- Disorder of copper metabolism
- Keyser-Fleischer ring: greenish brown ring of copper in Descemet membrane

TABLE 2-5 Metabolic Disorders

Disease	Inheritance	Gene Defect	Characteristic Ocular Finding
Alkaptonuria	Autosomal recessive	Homogentisic acid oxidase	Blue-black sclerae (Osler sign)
Fabry disease	X-linked recessive	α -galactosidase	Whorled corneal opacities
Wilson disease	Autosomal recessive	Copper transporter ATP7B	Keyser-Fleischer rings
Homocystinuria	Autosomal recessive	Cystathionine-beta-synthetase	Downward ectopia lentis
Richner-Hanhart syndrome (Tyrosinemia II)	Autosomal recessive	Hepatic tyrosine aminotransferase	Corneal clouding, pseudoherpetic corneal ulcers
Mucopolysaccharidoses	AR (Hunter’s XLR)	Varies	Corneal clouding, pigmented retinopathy in some

Homocystinuria (See Chapter 27)

- Autosomal dominant
- Deficiency of cystathionine-*beta*-synthetase (CBS)
- Downward lens dislocation (ectopia lentis)
 - Within first decade of life
- Myopia
- Rupture of the sclera and retinal detachment

Primary Amyloidosis (Myeloma-Associated) (Fig. 27-4)

- Amyloid protein (AL) derived from immunoglobulin light chains
- Periorbital purpuric plaques (“pinch purpura”)
- Amyloid deposition in the corneal stroma, conjunctiva and eyelid nodules
- Lattice corneal dystrophy

Richner-Hanhart Syndrome (Tyrosinemia II) (See Chapters 27, 30)

- Autosomal recessive
- Deficiency of hepatic tyrosine aminotransferase
- Eye lesions occur before skin lesions (2 weeks of age to 8 years of age)
- Corneal clouding and opacities, progressing to dendritic ulcers (pseudoherpetic)

- In contrast to herpetic ulcers, the lesions are bilateral; poor staining with fluorescein
- Neovascularization

Mucopolysaccharidoses (Hunter, Hurler, San Filippo, Schie, Morquio, Maroteaux-Lamy) (See Chapter 27)

- Autosomal recessive except for Hunter, which is X-linked recessive
- Corneal clouding, present at birth and most severe in Hurler and Schie
- Pigmented retinopathy (except for Morquio and Maroteaux-Lamy)
- Optic atrophy: most severe in Hurler

Gaucher Syndrome (See Chapters 11, 27)

- Autosomal recessive
- Acid- β -glucosidase gene 1q21
- Accumulation of glucocerebroside in tissues
- Pingueculae

Niemann-Pick Disease (See Chapter 27)

- Autosomal recessive
- Sphingomyelin phosphodiesterase-1
- Accumulation of sphingomyelin
- Cherry red spots in fovea
- Blindness

Tay-Sachs Syndrome

- Autosomal recessive
- Defect in hexosaminidase A
- Accumulation of ganglioside in tissues
- Cherry red spots in fovea

Biotinidase Deficiency (See Chapter 19)

- Autosomal recessive
- Biotinidase gene
- Optic atrophy

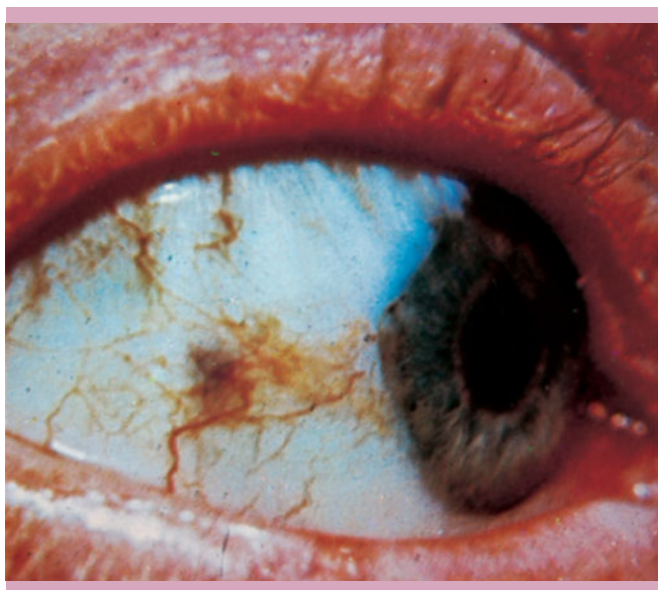


FIGURE 2-13 Alkaptonuria has pathognomonic ocular signs. The first to appear is grayish black scleral pigmentation anterior to the tendon insertions of the horizontal recti muscles. At times, pigmentation of the elastic tissue in pinguecula may stain a dark brown or black, and it usually has the configuration of small, dark rings. In advanced cases of ochronosis, Bowman's membrane, adjacent to the limbus, may have areas of black pigmentation. (Reproduced with permission from Wolff K et al., *Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

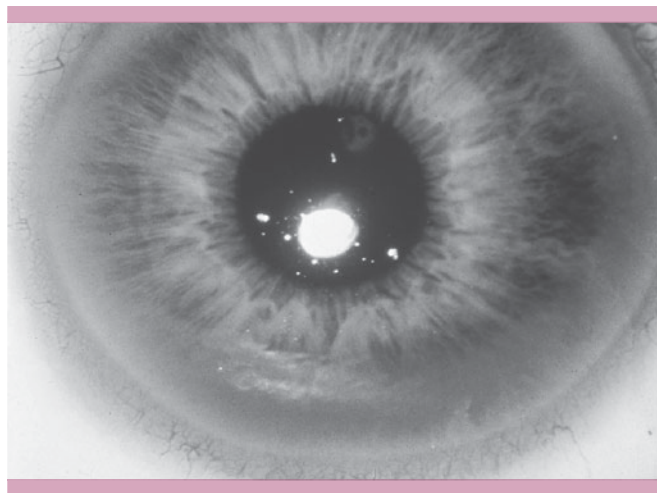


FIGURE 2-14 Hepatolenticular degeneration. (From Lowenstein J, Lee S: *Ophthalmology: Just the Facts*. New York: McGraw-Hill; 2004, p. 123.)

Generalized Sialidosis (Cherry-Red Spot-Myoclonus Syndrome)

- Lysosomal storage disease
- Color blindness or night blindness
- Cherry red spots
- Corneal or lens opacities

Xanthelasma Palpebrarum (Fig. 2-15)

- Asymptomatic bilateral and symmetric, yellow, flat, polygonal papules around the eyelids
- Most common in the upper eyelid near the inner canthus
- May be associated with isolated hyperlipidemia or familial syndromes
 - Familial hypercholesterolemia, familial defective Apo B, Familial dysbetalipoproteinemia
- Patients may be normolipemic
- Lesions characterized by accumulations of lipid-laden macrophages

Thyroid-Associated Ophthalmopathy (TAO) (See Chapter 27)

- Also known as Graves' ophthalmopathy
- Autoimmune-mediated inflammation of the extraocular muscle and periorbital connective tissue
- Dalrymple sign: upper lid retraction
- Eyelid retraction (can see sclerae superior to the iris), proptosis, chemosis, periorbital edema, and altered ocular motility (restrictive myopathy, usually of inferior rectus and medial rectus, resulting in hypotropia and esotropia and defective elevation and abduction), diplopia, congestion of orbit
- Exposure keratopathy is common and should be prevented
- Optic nerve damage with visual field loss can be gauged by relative afferent pupillary defects

ACNEIFORM CONDITIONS

Acne Rosacea

- Eyelid telangiectasias, blepharitis, recurrent chalazia, conjunctivitis, corneal scarring

VIRAL INFECTIONS

Varicella and Herpes Zoster Ophthalmicus (See Chapter 17)

- Varicella-zoster virus (VZV) (Fig. 2-16): Human herpes virus 3 (HHV3) that causes both varicella (chicken pox) and herpes zoster (shingles) Herpes zoster ophthalmicus occurs in later life and causes ocular complications and severe neuralgic pain
- More common in immunosuppressed individuals
- Ophthalmic branch of the trigeminal nerve is commonly involved



FIGURE 2-15 Xanthelasma. Multiple, longitudinal, creamy-orange, slightly elevated dermal papules on the eyelids of a normolipemic individual. (Reproduced with permission from Wolff K et al. *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 5th Ed. New York: McGraw-Hill; 2008.)



FIGURE 2-16 Varicella-zoster virus: ophthalmic herpes zoster. (From Wolff K et al. *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 5th Ed. New York: McGraw-Hill; 2005, p. 825.)

- Nasociliary branch involvement results in conjunctivitis, punctate keratitis, episcleritis and uveitis
- Hutchinson's sign: involvement of nasal tip or nasal sidewall, innervated by the external nasal nerve; signifies potential ocular involvement
- Prodrome of pain over the affected dermatome
- Eruption may present as maculopapular, vesiculopapular, ulcerative, and may form a crust with possible scarring
- No correlation between severity of skin eruption and severity of ocular involvement
- Ocular complications such as keratitis and uveitis occur in 50% of patients with cutaneous eruption and appear within 3 weeks of developing rash

- Anterior uveitis is treated with topical steroids and cycloplegics
- Acute retinal necrosis has been reported following chicken pox and herpes zoster infection in healthy patients
- Cranial nerve palsies may occur; oculomotor (CNIII) nerve most commonly affected

Herpes Simplex Keratitis (See Chapter 17)

- Primary ocular herpes occurs as a follicular conjunctivitis, regional lymphadenitis, and ulcerative blepharitis
- Recurrent episodes of keratitis are common
- Dendritic corneal ulcers are pathognomonic
- Recurrent stromal keratitis causes structural damage to cornea resulting in corneal opacities often requiring corneal transplant
- Most common cause of corneal blindness in the United States

Molluscum Contagiosum (See Chapters 8 and 17)

- Small, waxy nodules have a central umbilication
- If present on the eyelids, they may produce a follicular conjunctivitis

Rubella (See Chapter 17)

- When congenital, cataracts may develop (bilateral in 75% of patients)

Measles (Rubeola) (See Chapter 17)

- Conjunctivitis (part of the 3 C's: cough, coryza, conjunctivitis and Koplik spots)
- Koplik spots may be seen on the conjunctiva

Mumps

- Dacryoadenitis (inflammation of lacrimal glands)

Vaccination

- Optic neuritis may occur following certain vaccinations
- MMR vaccination most common
- Onset within 2 weeks
- Bilateral vision loss; pain with eye movement can also occur
- Treatment is oral corticosteroids
- Prognosis: complete recovery

BACTERIAL DISEASES

Oculoglandular Syndrome of Parinaud (See Chapter 15)

- Cat-scratch disease (*Bartonella henselae*)
- Unilateral granulomatous conjunctivitis

Syphilis (See Chapter 15)

- Caused by the spirochete *Treponema pallidum*

- *Congenital syphilis*: interstitial keratitis
- *Secondary syphilis*: anterior uveitis
- *Neurosyphilis*: argyll Robertson pupil: small, irregular pupil that reacts normally to accommodation but not to light

Miliary Tuberculosis (See Chapter 15)

- Caused by *Mycobacterium tuberculosis*
- Occurs when caseous material reaches the bloodstream from a primary focus
- Can cause choroidal tubercles in the retina (discrete yellow nodules)

Leprosy (See Chapter 15)

- Caused by *Mycobacterium leprae*
- 20–50% of leprosy patients with ocular involvement (mostly patients with lepromatous leprosy)
- If left untreated, leads to blindness
- In those affected: loss of eyebrows (71%), diminished sensitivity of cornea (63%), lagophthalmos (inability to close the eye, more common in tuberculoid leprosy) (44%), madarosis (41%)

Lyme Disease (See Chapter 15)

- Caused by *Borrelia burgdorferi*
- Transmitted by the bite of an infected *Ixodes* tick
- Stage 1: conjunctivitis and photophobia
- Stage 2: CN VII palsy (Bell palsy), blurred vision due to papilledema, optic atrophy, optic or retrobulbar neuritis, or pseudotumor cerebri
- Stage 2 or stage 3: episcleritis, symblepharon, keratitis, iritis, pars planitis, vitreitis, chorioretinitis, exudative retinal detachment, retinal pigment epithelial detachment, cystoid macular edema, and branch artery occlusion

Actinomyces (See Chapter 28)

- *Actinomyces israelii* is a gram-positive anaerobic bacillus; found in soil, brackish water
- *Actinomyces keratitis* (keratoactinomycosis)
- In the US, keratitis associated with contact lens use, especially when tap water used to cleanse lenses
- Dry ulceration with central necrosis surrounded by a gutter of demarcation
- Conjunctivitis, blepharitis
- Primary chronic canaliculitis of tear drainage apparatus
- 30% have negative cultures; culture of contact lens case may reveal organism

Hordeolum (See also above text)

- External hordeolum (stye)
- Arises from a blockage and infection of Zeiss or Moll sebaceous glands
- Abscess points at the lid margin
- Internal hordeolum

- Secondary infection of meibomian glands in the tarsal plate
- *Staphylococcus aureus* is the infectious agent in 90–95% of cases

FUNGAL DISEASES

Candidiasis (See Chapters 4 and 22)

- 2/3 patients with systemic candidiasis have ocular involvement
- White exudative lesions in the vitreous signifying necrotizing granulomatous retinitis
- “String of pearls” on exam signifies spread to vitreous cavity
- Requires intravitreal therapy

Mucormycosis (See Chapter 4)

- Occurs in immunocompromised patients, especially poorly controlled diabetics
- Rhizopus, Mucor, Absidia
- Pathognomonic black hemipalate, proptosis
- Blindness may occur from ophthalmic artery occlusion

INFESTATIONS, BITES, PARASITIC DISEASES

Onchocerciasis (River Blindness) (See Chapter 5)

- Onchocerca volvulus
- Simulium black fly vector
- Microfilariae in the anterior chamber
- Sclerosing keratitis, chorioretinitis, glaucoma, blindness

Loias (See Chapter 5)

- Filarial nematode: *Loa loa*
- Bite from *Chrysops*
- Calabar swellings: localized areas of angioedema
- Migration of adult worm across conjunctiva

Pediculosis Pubis (See Chapters 5 and 22)

- Occasionally, infestation may be present in the eyebrows and eyelashes

Toxoplasmosis

- Congenital
- 1/3 of exposed infants are affected
- Chorioretinitis

DERMATOUVEITIDES

Behçet Disease

- HLA-B5, -B51

- Major criteria
 - Recurrent oral aphthous ulcers (at least 3 in a 12-month period)
- Minor criteria (2/4)
 - Pathergy
 - Ocular findings: anterior uveitis, posterior uveitis, retinal vasculitis
 - Genital ulcers
 - Skin findings: pustules, erythema nodosum
 - Patients may complain of decreased visual acuity from severe uveitis, pain, redness, photophobia
 - Neovascular glaucoma, cataracts, vitreous hemorrhage, iritis, retinal vessel occlusions, and optic disc edema
 - Anterior uveitis: most common eye abnormality overall (a third of cases)
 - Hypopyon uveitis: pus in the anterior chamber
 - Posterior uveitis with retinal vasculitis is the most common cause of blindness
 - Treatment involves immunosuppressants for eye involvement such as azathioprine or cyclosporine A

Reiter Syndrome (See Chapter 11)

- HLA-B27
- Conjunctivitis is most common eye finding
- Uveitis may progress to visual impairment

VITAMIN-RELATED DISORDERS

Vitamin A Deficiency (See Chapter 19)

- Night blindness, dryness, corneal ulceration/keratomalacia, HSV infection
- Bitot’s spots: foamy areas on conjunctiva from accumulation of keratin or bacteria

Vitamin B Deficiency (See Chapter 19)

- B1 (Beriberi)
 - Thiamin deficiency
 - 70% have ocular abnormalities: dry eyes, vision loss from optic nerve atrophy
- B2
 - Riboflavin deficiency
 - Rosacea keratitis, seborrheic blepharitis, secondary conjunctivitis

Vitamin C Deficiency (See Chapter 19)

- Scurvy
- Ocular features include those of Sjögren syndrome, as well as subconjunctival hemorrhage and hemorrhage within the optic nerve sheath

QUIZ

Questions

1. What syndrome has angiod streaks (and what does this finding represent)?
2. In what syndromes can blue sclerae be found?
3. Glaucoma is associated with:
 - A. Neurofibromatosis 1
 - B. Neurofibromatosis 2
 - C. Sturge-Weber syndrome
 - D. PHACES syndrome
 - E. Biotinase deficiency
4. Which syndrome has downward ectopia lentis?
 - A. Homocystinuria
 - B. Marfan's syndrome
 - C. Nail patella syndrome
 - D. Focal dermal hypoplasia (coloboma)
5. Matching:

i. Phakoma	A. Neurofibromatosis 1
ii. Retinal hemangio-blastoma	B. Hyperpigmentation of papillary margin
iii. Comma-shaped corneal opacity	C. Von-Hippel-Lindau syndrome
iv. Lester iris	D. X-linked ichthyosis
v. Lisch nodule	E. Astrocytic hamartomas of optic nerve
6. In what two syndromes can a "salt-and-pepper" retina be seen?
7. What is the most common epithelial tumor of the eyelid?
 - A. Basal cell carcinoma
 - B. Squamous cell carcinoma
 - C. Sebaceous cell carcinoma
 - D. Melanoma
 - E. Merkel cell carcinoma
8. A young patient presents with brittle bones resulting in easy fractures with minor trauma as well as easy bruising. A common eye finding is:
 - A. Comma-shaped corneal deposits
 - B. Ectropion
 - C. Blue sclera
 - D. Cataracts
 - E. Lisch nodules
9. An elderly female patient presents with a painless subcutaneous module on the right upper eyelid. She was treated with warm compresses and topical

antibiotics for several weeks without any improvement. The biopsy showed sebaceous differentiation, prominent atypia, with pagetoid spread. What is your diagnosis?

- A. Merkel cell carcinoma
 - B. Sebaceous adenoma
 - C. Melanoma
 - D. Sebaceous cell carcinoma
 - E. Basal cell carcinoma
10. Apocrine glands along the eyelid are called:
 - A. Zeis glands
 - B. Meibomian glands
 - C. Glands of Moll
 - D. Montgomery glands
 - E. Fordyce spots

Answers

1. Pseudoxanthoma elasticum; represents rupture of Bruch's membrane.
2. Osteogenesis imperfecta, types 1, 2, 3; Ehlers-Danlos syndrome, type 6 (other findings are retinal detachment, ruptured globe, keratoconus); reported in Crouzon syndrome.
3. A and C.
4. A. Marfan's syndrome associated with upward ectopia lentis, nail patella syndrome associated with Lester iris, focal dermal hyperplasia associated with coloboma.
5. i-E. Phakoma. Astrocytic hamartomas of the retina or optic disc are typical lesions in patients with tuberous sclerosis. They are detected by angiography. They are usually benign and appear as white/gray nodular lumps.
 ii-C. Von Hippel-Lindau (VHL) syndrome is characterized by hemangioblastomas of the brain, spinal cord, and retina. VHL syndrome is autosomal dominant and is due to a mutation in the VHL tumor suppressor gene.
 iii-D. X-linked ichthyosis is associated with comma-shaped corneal opacities that may be evident with slit lamp examination. X-linked ichthyosis most typically appears in infancy with scaling on the posterior neck, upper trunk and extensor surfaces of the extremities.
 iv-B. Hyperpigmentation of the papillary margin is the description of Lester iris. Nail patella syndrome (hereditary osteocnchodysplasia) is an autosomal dominant disorder with a mutation in the gene encoding transcription factor LMX1B. The main clinical findings include fingernail dysplasia, absent or hypoplastic patellae, the presence

of posterior conical iliac horns, and deformation of the radial heads. Lester iris occurs in 45% of patients with nail patella syndrome.

v-A. Neurofibromatosis 1 (NF-1). NF-1 is diagnosed if two or more of the following are present:

1. Six or more café-au-lait spots, 15-mm or larger in an adult; six or more café-au-lait spots, 5-mm or larger in a prepubescent child
2. Two or more neurofibromas or one plexiform neurofibroma
3. Freckling of the axillary or inguinal region, an optic pathway glioma, two or more Lisch nodules
4. Characteristic osseous lesions, such as sphenoid wing dysplasia
5. A first degree relative with NF-1

Lisch nodules are the most common type of ocular involvement in NF-1. They are melanocytic hamartomas, usually clear yellow or brown elevations that project from the surface of the iris. Slit lamp is the ideal method to evaluate them.

6. Cockayne syndrome, refsum syndrome.
7. A. Basal cell carcinoma is the most common tumor of the eyelid. The most common location is the lower eyelid (48.9–72.1%). Sebaceous cell carcinoma has a predilection for the upper eyelid. Melanoma is a rare pigmented eyelid tumor. Merkel cell carcinoma usually affects the upper eyelid. Squamous cell carcinoma occurs in 5% of malignant eyelid tumors.
8. C. Blue sclera. The patient has osteogenesis imperfecta. Type 1 collagen is the defective protein. Mutations of COL1A1 and COL1A2 causes defects in pro-alpha 1 and pro-alpha 2 chains that impose type 1 collagen. Blue sclera is also found in the following disorders: progeria, cleidocranial dysplasia, Menkes syndrome, cutis laxa, Cheney syndrome and pyknodysostosis.
9. D. Sebaceous carcinoma (SC). Sebaceous carcinoma occurs most commonly in a periocular (75%) location. The most frequent clinical presentation is a painless subcutaneous nodule; it is often misdiagnosed as a chalazion or chronic blepharitis. Histologically, SCs may be classified as well, moderately, or poorly differentiated. They show sebaceous differentiation, prominent atypia with pagetoid spread. The tumors have high rates of recurrence and metastasis. Mortality ranges from 9% to 50%. The tumors are associated with Muir-Torre syndrome.
10. C. Glands of Moll. Glands of Moll are apocrine glands located anterior to the meibomian glands

within the distal eyelid margin. Zeis glands and meibomian glands are both sebaceous glands of the eyelid. Montgomery's glands are sebaceous glands in the areola. Fordyce spots are ectopic sebaceous glands found on the vermillion lip and/or genital area.

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NAIL FINDINGS

RAVI UBRIANI

NAIL ANATOMY (FIG. 3-1)

- Nail plate
 - Forms from keratinization of the nail matrix epithelium and is firmly attached to the nail bed
 - Dorsal nail plate is produced by the nail matrix
 - Ventral portion is produced by the nail bed
 - Nail thickness depends on the length of the nail matrix and nail bed
 - Pink color owing to underlying nail bed blood vessels
 - Onychocorneal band: most distal portion of firm attachment of the nail plate to the nail bed
 - Onychodermal band: pink band that lies between the onychocorneal band and the nail plate white free edge
- Proximal nail fold
 - Dorsal portion: thinner than skin of the digit, devoid of pilosebaceous units
 - Ventral portion: in continuity with the matrix, adheres to the nail plate surface, and keratinizes with a granular layer
 - Horny layer forms the cuticle and prevents the separation of the plate from the nail fold
 - Dermis contains numerous capillaries that run parallel to the surface of the skin; morphology can be altered in connective tissue diseases
- Nail matrix
 - Lies above the midportion of the distal phalanx
 - Keratinization of the proximal nail matrix cells produces the dorsal nail plate
 - Keratinization of the distal nail matrix cells produces the ventral nail plate
 - Lunula: where the distal matrix is not completely covered by the proximal nail fold but is visible through the normal nail plate as a white half-moon-shaped area
- Cells are able to synthesize both “soft,” or skin-type, and “hard,” or hair-type, keratins – the matrix expresses keratins Ha1, K1, K10
- Alteration in the color of lunula can be an indication of either a cutaneous or systemic disorder or a systemic drug side effect
- Nail bed
 - Extends from the distal margin of the lunula to the onychodermal band
 - Completely visible through the nail plate
 - Epithelium is adherent to the nail plate, two to five cell layers
 - Nail bed keratinization produces a thin horny layer that attaches to the ventral nail plate
 - The bed expresses keratins K6, K16, K17
 - No granular layer is present
- Hyponychium
 - Anatomic area between the nail bed and the distal groove, where the nail plate detaches from the dorsal digit
- Dermis
 - No subcutaneous tissue, no pilosebaceous units
 - Condensed connective tissue that forms a tendon-like structure connecting the matrix to the periosteum of the phalangeal bone
- Blood and nerve supply
 - Blood supply provided by the lateral digital arteries, arches supply the matrix and nail bed
 - Sensory nerves: originate from the dorsal branches of the paired digital nerves, run parallel to the digital vessels
- Nail growth
 - Fingernails: 3 mm/month, 0.1 mm/day, take 5–6 months to regrow
 - Toenails: 1 mm/month, 0.03 mm/day, take 12–18 months to regrow
 - After nail plate is avulsed, it takes 40 days before new fingernail will first emerge

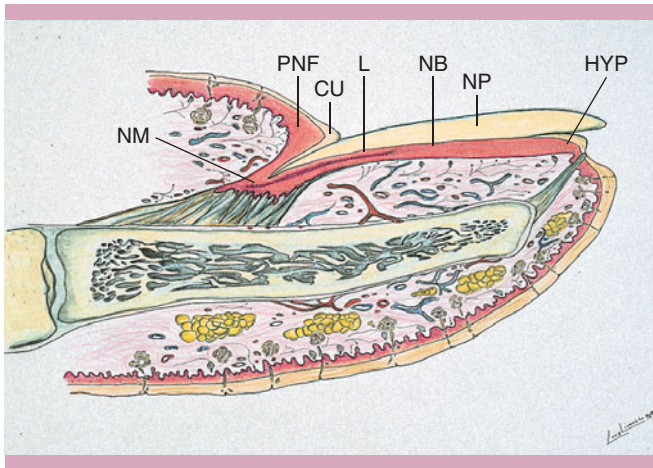


FIGURE 3-1 Drawing of a normal nail. CU, cuticle; HYP, hyponychium; L, lunula region; NB, nail bed; NM, nail matrix; NP, nail plate; PNF, proximal nail fold. (From Freedberg IM et al. *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003, p. 159.)

NAIL DISORDERS

Chromonychia

- Abnormality in color of the substance and/or the surface of the nail plate and/or subungual tissue
 - Systemic cause: all digits are usually involved
 - Endogenous cause: edge of color corresponds to shape of lunula (concave)
 - External contact: edge of color follows the shape of the proximal nail fold (convex)
1. Blue lunula
 - Causes of this condition include
 - Wilson's disease
 - Argyria, silver nitrate
 - Drugs: azidothymidine (AZT), quinacrine, busulfan, phenolphthalein
 2. Red lunula (Fig. 3-2)
 - Causes of this condition include
 - Cardiac failure
 - Rheumatoid arthritis
 - Alopecia areata
 - Lupus
 - Polycythemia vera
 - Carbon monoxide poisoning
 3. Leukonychia
 - Can be caused by defective keratinization of the distal matrix with persistent parakeratosis in the ventral nail plate
 - White color of nail in five patterns: total leukonychia (inherited usually), distal portion still appears pink, transverse leukonychia (systemic disorder), punctate (from minor trauma), longitudinal (associated with Darier's disease)
 4. Longitudinal melanonychia (Fig. 3-3)
 - Presence of a pigmented stripe, usually brown or black
 - Deposition of melanin in the nail plate from a variety of causes
 - Melanotic macule is the most common cause
 - Bands of nevocellular nevi
 - Nevi, pigmented fungal infections, or melanoma
 - Drugs
 - ▲ azidothymidine (AZT): develops between 8 weeks to 1 year
 - ▲ antimalarials
 - Laugier-Huntziker syndrome (findings include longitudinal melanonychia, and macular pigmentation of the lips, mouth, and anogenital area)
 - Trauma
 - Pregnancy
 - Radiation-induced
 - Inflammatory nail disorders (lichen planus, onychomycosis, chronic radiation dermatitis, pustular psoriasis, or Hallopeau's disease)
 - Systemic diseases: Acquired immune deficiency syndrome (pigmentation unrelated to AZT treatment), Addison's disease, Cushing's



FIGURE 3-2 Red lunula. (Courtesy of Dr. Adelaide Hebert.)



FIGURE 3-3 Longitudinal melanonychia. (Courtesy of Dr. Ravi Ubriani.)

- syndrome, hyperthyroidism, hemosiderosis, hyperbilirubinemia, alkaptonuria, systemic lupus erythematosus, scleroderma and porphyria
- Nutritional disorders
 - vitamin B12 or folate deficiency
 - bluish-black pigmentation
 - pigmentation is completely reversible after correction of the vitamin deficiency
- 5. Subungual melanoma
 - Broad band, dark brown to black in color with indistinct lateral borders
 - 0.7–3.5% of cutaneous melanomas. Most common type of melanoma in Asian and African-American populations – the rate is the same as in Caucasian populations, but is overrepresented because the frequency of other types of melanoma is low
 - Longitudinal black or brown bands with different hues
 - Commonly affects thumbs and great toes
 - Hutchinson's sign: spread of pigmentation onto the nail folds
 - Pigmentation in a single digit, especially the index finger, thumb or great toe
 - Usually occurs at age 50 or older
- 6. Subungual hemorrhage (Fig. 3-4)
 - Reddish to reddish-black pigment depending on the age of the bleed
 - Progressively grows out distally as the nail plate grows
 - Can be due to trauma
 - Nail tumors can be preceded by or first recognized after trauma and may bleed



FIGURE 3-4 Subungual hemorrhage. (Courtesy of Dr. Asra Ali)

- May need to be biopsied to rule out subungual melanoma if hemorrhage does not grow out with the nail or if it recurs at the same place

External Factors Causing Nail Disorders

1. Habit-tic deformity (Fig. 3-5)
 - Multiple transverse grooves (Christmas-tree pattern) with a central depression
 - Usually affects thumbnails
 - Chronic mechanical injury to the cuticle and underlying matrix
2. Onychogryphosis (Fig. 3-6)
 - Curved, thickened nail plate without attachment to the nail bed
 - Opaque, yellow-brown with an oyster shell appearance
 - Nail keratin is produced by the nail matrix at uneven rates, with the faster-growing side determining the direction of the deformity
 - Ill-fitting footwear, self-neglect, trauma, age, occasionally inherited as an autosomal dominant trait
 - Hemionychogryphosis with lateral deviation of the nail plate results from congenital malalignment of the big toenail
3. Onycholysis
 - Separation of the nail plate from the bed
 - Yeast and bacteria usually colonize underlying space



FIGURE 3-5 Habit tic. (Courtesy of Dr. Ravi Ubriani.)



FIGURE 3-6 Onychogryphosis. (Courtesy of Dr. Richard Krathen.)

- Primary causes
 - Trauma
 - Idiopathic
- Secondary
 - Dermatologic and systemic conditions: onychomycosis, diabetes mellitus, thyroid disorders, pregnancy, porphyria, pellagra, scurvy, psoriasis, scleroderma, lupus, hidrotic ectodermal dysplasia, chronic contact dermatitis, pompholyx, herpes simplex, sarcoidosis, amyloidosis
 - Photo-induced onycholysis: tetracyclines (demecycline highest, doxycycline next, minocycline least), psoralens, 8-MOP, fluoroquinolones, chloramphenicol
 - Nail bed tumors
 - Congenital
- Treatment: Remove underlying cause. If traumatic, emphasize non-traumatic nail practices and reduce network. Concurrent use of topical anti-yeast medications can reduce colonization and hasten reattachment. There is not a role for oral antifungals. In cases of single resistant onycholysis, examination of the underlying nailbed with biopsy may be necessary to rule out underlying malignancy
- 4. Onychoschizia/brittle nails
 - Splitting of the free edge and distal portion of the nail plate impairment of intercellular adhesive factors of the nail plate
 - May also include breaking of the lateral edges, causing transverse splitting
 - Causes of onychoschizia consist of external factors that dissolve or break the coherence between corneocytes: immersion/desiccation, chemicals, trauma, fungi
- Treatment: in some cases, reduction in use of nail cosmetics may be helpful. Oral supplementation with biotin or silicone may be helpful as well
- 5. Splinter hemorrhages
 - Red to black small thin longitudinal lines under the nail plate
 - Most commonly located in the distal nail plate
 - Disruption of longitudinal blood vessels in the nail bed
 - Caused by injury to the nail (most common cause) or by certain drugs, and/or inflammatory nail disorders
 - Resolves spontaneously
 - Treatment: if no underlying cause, reassurance as to benign nature of condition. Otherwise, treat underlying condition
- 6. Ingrown nails
 - Great toenails are particularly vulnerable
 - Improper nail trimming, tight shoes, or poor posture can cause a corner of the nail to curve downward into the skin
 - Can lead to inflammation, granulation tissue formation, and infection
 - Treatment: non-surgical treatments try to separate the lateral nail fold from the nailplate with barriers or by taping the lateral nail fold away from the plate. Surgical treatment includes phenol destruction of the lateral part of the nail plate leading to a narrowed nail. In acute cases, antibiotics and/or drainage of purulent collection may be necessary
- 7. Transverse overcurvature (Pincer or Trumpet nail)
 - Nail displays an increase in curvature along the nail bed
 - May be associated with subungual exostosis
 - Overcurvature may extend to the point of encompassing a cone of nail bed soft tissue

- Treatment: non-surgical bracing treatments can slowly flatten the nailplate. Surgical treatment includes phenol destruction of the lateral part of the nail plate leading to a narrowed nail. In acute cases, antibiotics and/or drainage of purulent collection may be necessary
8. Chronic paronychia (Fig. 3-7)
- Inflammation of the proximal nail fold with painful periungual erythema
 - Nail detaches from the distal portion of the proximal nail fold, which has lost its cuticle
 - May result in *Candida* invasion with discolored nail plate and cross-ridged lateral edges
 - Can be acute or chronic
 - Acute: usually caused by infection (see nail infection section below)
 - Chronic: Occurs in patients whose hands are subjected to moist local environments or in patients who damage the cuticle through traumatic nail practices. Thought to be an irritant or allergic contact dermatitis of the proximal nail fold due to entry of irritants or allergens under the proximal nail fold after loss of the cuticle



FIGURE 3-7 Chronic paronychia. (Courtesy of Dr. Ravi Ubriani.)

- Can be a side effect of epidermal growth factor receptor inhibitors
 - Treatment: acute cases: (see nail infection section below); chronic cases: reduction of wetwork and contact with irritants and discontinuation of traumatic nail practices is necessary. Short-term use of high-potency topical steroids. Topical anti-yeast medications have become less favored, but can be used in addition. Oral antifungal medications should not be used as single therapy, but have not been disproven as adjuncts to above therapy
9. Onychomadesis (nail shedding)
- Spontaneous separation of the nail plate from the nail bed beginning from the proximal nail end
 - Associated with: systemic lupus erythematosus, pemphigus vulgaris, mycosis fungoides, alopecia areata universalis, epidermolysis bullosa, keratosis punctata palmaris et plantaris, thrombocytopenia, neurologic disease, peritoneal dialysis, penicillin anaphylaxis, chemotherapy, retinoids (dose related nail matrix damage), lead intoxication, and carbamazepine
 - When associated with systemic illness, generalized skin disease, or drug therapy the condition may be considered a severe form of Beau's lines. (temporary slowing or cessation of nail plate production)
 - Nail plate shows a transverse split but continues growing for some time
 - Eventually the nail is cast off after losing the connection to the underlying nailbed
 - Treatment: Reassurance as to eventual resolution if related to a one-time event. Treat underlying cause if still active or related to an underlying disease

Genetic Syndromes

1. Keratosis follicularis (Darier's disease) (Fig. 3-8)
 - Autosomal dominant
 - Defect in ATPase 2A2, which encodes sarco (endo)plasmic reticulum Ca^{2+} -ATPase (SERCA2), a calcium pump
 - Nails: red and white longitudinal streaks, wedge-shaped nicking of the distal nail plate, subungual hyperkeratosis
 - May be related to acrokeratosis verruciformis of Hopf (acral Darier's disease): multiple warty lesions resembling plane warts typically observed on the dorsum of the hands and feet
2. Nail-patella syndrome
 - Also known as HOOD or Fong syndrome
 - Autosomal dominant



FIGURE 3-8 Darier nail. (Courtesy of Dr. Adelaide Hebert.)

- Defect in *LMX1B* gene
 - Nails: triangular lunula, hypoplasia of nails, may involve all fingernails (thumbs are the most severely affected)
 - Hypoplastic or absent patella, bilateral posterior iliac horns, radial head subluxation, scoliosis, palmoplantar hyperhidrosis
 - Glomerulonephritis \pm renal failure
 - Eyes: heterochromic irides, Lester iris, cataract
3. Dyskeratosis congenita
 - X-linked form associated with *DKC1* gene, located at Xq28, encodes for *dyskerin* protein (essential in ribosome biogenesis and telomerase assembly)
 - Autosomal dominant form associated with *hTERT* gene
 - Classical tetrad of progressive bone marrow failure, reticulated skin hyperpigmentation, nail dystrophy, and oral leukoplakia
 - Nails: ridging, longitudinal fissuring, thin and dystrophic – first component of syndrome to appear
 4. Congenital malalignment
 - Lateral deviation of the long axis of nail growth relative to the distal phalanx
 - Subsequent ingrowing and possible hemionychogryphosis if untreated
 - Acquired traumatic malposition may follow acute trauma
 5. Hereditary ectodermal dysplasia
 - Primary epidermal disorders in which one of the following signs occur: hypotrichosis, hypodontia, onychodysplasia, and anhidrosis
 - Nails are most commonly short, thickened, and hypoplastic
 6. Epidermolysis bullosa (EB)
 - Junctional and dystrophic forms may produce anonychia
- Abnormalities of the nail matrix and nail bed associated with the pathologic genetic alterations of the dermal-epidermal junction
7. Pachyonychia congenita (PC)
 - Autosomal dominant
 - Nail changes: Severe nail thickening, yellow-gray color, transversely overcurved with subungual hyperkeratosis mainly at the distal portion of the nails
 - Two main clinical subtypes, PC-1 and PC-2, and other rare variants
 - Type I PC: Jadassohn-Lewandowsky (more common)
 - ▲ Keratins 6a and 16 defects
 - ▲ Palmoplantar and follicular hyperkeratosis, benign oral leukoplakia
 - Type II PC: Jackson-Lawler
 - ▲ Keratins 6b and K17 defects
 - ▲ Type I PC symptoms plus bullae on palms and soles, early dentition/natal teeth, steatocystoma multiplex
 - Type III: Shafer-Branauer
 - ▲ Type I symptoms plus corneal dystrophy, cataracts
 - Type IV: pachyonychia congenita tarda
 - ▲ Late onset, hyperpigmentation around the neck, waist, and flexures

Infections of the Nails

1. Onychomycosis (Fig. 3-9)
 - Clinical features depend on type of infection present
 - Distal subungual onychomycosis: *Trichophyton rubrum*, *Trichophyton interdigitale*
 - ▲ Distal onycholysis with subungual hyperkeratosis, and yellow discoloration
 - Proximal subungual onychomycosis: *T. rubrum*, *Fusarium* sp., *Aspergillus* sp., *Scopulariopsis* sp.
 - ▲ Proximal leukonychia with normal nail plate surface
 - ▲ Associated with AIDS
 - Superficial white onychomycosis: *Trichophyton interdigitale*, *Fusarium* sp., *Aspergillus* sp.
 - ▲ Superficial areas of friable opaque leukonychia
 - ▲ More common in children and HIV-positive individuals
 - Treatment: oral antifungals or topical antifungal nail lacquer should be used if no contraindications with appropriate laboratory monitoring
2. Green nails (*Pseudomonas* nail infection) (Fig. 3-10)
 - *Pseudomonas aeruginosa* (gram negative bacteria) can infect the dorsal or ventral nail plate of the nail



FIGURE 3-9 Onychomycosis. (Courtesy of Dr. Adelaide Hebert.)

- Presents with green (pyocyanin) or yellow (fluorescein) nail pigmentation
 - Can happen more frequently to patients with underlying onycholysis or onychomycosis
 - Treatment: topical vinegar soaks, floxacillin, or gentamicin can be used to treat the infection. Treat underlying condition if onycholysis or onychomycosis is present
3. Acute paronychia (Fig. 3-11)
- Associated with direct or indirect trauma to the cuticle or nail fold
 - May start in the paronychium (lateral nail fold) at the side of the nail with local redness, swelling, and pain
 - Most common causative pathogen is *Staphylococcus aureus*, less commonly *Streptococcus pyogenes*, *Pseudomonas pyocyanea*, *Proteus vulgaris*, or herpes simplex virus
 - Treatment: incision and drainage with culture and appropriate antibiotics for staph and strep infection. Consideration should be given to diagnostic procedures for HSV as acute paronychia can be caused by HSV

Nail Signs of Systemic Disease

1. Nail pitting
- Depressions in the nail plate that vary in morphology and distribution
 - Characteristic of psoriasis, alopecia areata, and eczema
 - Easily detachable parakeratotic cells in the superficial layers of the nail plate, as the nail plate grows outwards, these parakeratotic foci are exposed to the surrounding environment and there is a gradual sloughing of these cells, leaving a distinct depression within the nail plate



FIGURE 3-10 *Pseudomonas* nail. (Courtesy of Dr. Richard Krathen.)



FIGURE 3-11 Acute paronychia. (Courtesy of Dr. Robert Jordon.)

- Indicates a disturbance in the maturation and keratinization of the proximal nail matrix
- Alopecia areata (Fig. 3-12)
 - Nail findings are seen in 20% of adults and 50% of children
 - Geometric nail pitting (most common); pits are small and regularly distributed along longitudinal and transverse lines
 - Twenty nail dystrophy or trachyonychia (generalized nail roughness) seen mainly in patients with alopecia totalis or alopecia universalis



FIGURE 3-12 Nail pitting. (Courtesy of Dr. Robert Jordon.)



FIGURE 3-13 Lichen planus. (Courtesy of Dr. Asra Ali.)

- Psoriasis
 - Deep and irregularly distributed pits
 - Atopic dermatitis
 - Deep and irregularly distributed pits
 - Treatment: topical psoriasis medications applied to the proximal nail fold or injection of steroid into the proximal matrix may be helpful, but side effects may limit use to only the most motivated patients
2. Koilonychia
 - Nail plate is concave with raised edges (spoon nails)
 - Iron-deficiency anemia associated with Plummer-Vinson syndrome
 - Normal finding in childhood
 - Can be seen in patients with Mal de Maleda (keratoderma palmoplantaris transgrediens): painful glove-and-stocking keratoderma, psoriasiform hyperkeratotic plaques, koilonychia, onychogryphosis, fissured tongue/lingua plicata
 3. Lichen planus (Fig. 3-13)
 - Affects one or more nails in 10% of cases
 - Nail changes include: ridging, distal splitting, thinning, subungual hyperkeratosis, pterygium formation (adhesion of the proximal nail fold to the proximal nail bed), and possible loss of the nail
 - Treatment: injections of steroid or systemic prednisone may be necessary to prevent development of pterygium, but side effects must be balanced on an individual basis
 - Histology mirrors that of lichen planus in the skin, demonstrating a lichenoid infiltrate with apoptosis of keratinocytes. Spongiosis, focal parakeratosis, and scarring are more common in lichen planus of the nails
 4. Lindsey's nail (half-and-half nail)
 - Distal nail bed: brown to pink; proximal nail bed (40–80%) white
 - Associated with the following conditions: Azotemia, chronic renal failure with uremia
 5. Mees' lines
 - Transverse white bands
 - Grow out with nail
 - Appear after an episode of poisoning with arsenic, thallium or other heavy metals
 6. Muehrcke's lines
 - Nonspecific finding that may be associated with periods of metabolic stress, which transiently impairs the ability of the body (and particularly of the liver) to synthesize proteins
 - Paired white bands parallel to the lunula, and do *not* grow out with nail
 - Associated with: hypoalbuminuria, nephritic syndrome, chemotherapy, malnutrition, cirrhosis
 7. Nail fold telangiectasias (nailfold capillary loops)
 - Can be visualized by nailfold capillaromicroscopy or dermatoscopy
 - Dermatomyositis: enlargement of capillary loops, loss of capillaries, disorganization of the normal distribution of capillaries, 'budding' ('bushy') capillaries, twisted enlarged capillaries and capillary hemorrhages
 - Scleroderma (SSc): architectural disorganization, giant capillaries, hemorrhages, loss of capillaries, angiogenesis and avascular areas found in > 95% of patients

- Systemic lupus erythematosus: morphological alterations of capillary loops, venular visibility and sludging of blood with variability of capillary loop length
 - Anti-phospholipid syndrome: symmetrical microhemorrhages
 - Sjogren's syndrome: abnormalities range from non-specific findings (crossed capillaries) to more specific findings (confluent hemorrhages and pericapillary hemorrhages) or SSc-type findings
8. Terry's nail
- 1- to 2-mm distal pink band, proximal nail is opaque (white, ground-glass-like opacity)
 - Lunula is obliterated
 - Associated with hepatic failure, hyperthyroidism, malnutrition, liver cirrhosis, hypoalbuminemia congestive heart failure, diabetes mellitus
9. Twenty-nail dystrophy (trachyonychia)
- Term used to describe nail plate roughness, pitting, and ridging that may affect 1 to 20 nails
 - Autosomal dominant inherited form: present at birth and gets worse with age
 - Alopecia areata, psoriasis, lichen planus, atopic dermatitis, ichthyosis vulgaris, immunoglobulin A deficiency, or idiopathic
 - Histology demonstrates spongiosis most often
10. Yellow-nail syndrome (YNS) (Fig. 3-14)
- Pathogenesis unknown, lymphatic vessel alterations may play a role in some cases
 - Spontaneous partial or total remission in 7–30% of cases, however, relapse often occurs
 - Nail improvement is often concomitant with improvement of the respiratory pathology
 - Characterized by the triad of characteristic nail changes, chronic respiratory disorders (bronchiectasis, pleural effusion, bronchial hyperresponsiveness, bronchiectasis, chronic bronchitis) and primary lymphedema
11. Psoriasis
- Affects 10–55% of adults
 - Nail matrix disease: pitting (most common nail finding), leukonychia, red spots in lunula, nail plate crumbling, Beau's lines (occurs in lesions of the matrix of short duration, often caused by intermittent inflammation), onychorrhexis (occurs in lesions of the matrix of long duration)
 - Nail bed disease: oil drop [salmon patch] discoloration (due to psoriatic lesions contained entirely within the nail bed that can be seen through the overlying nail plate), onycholysis, nail bed hyperkeratosis (from the deposition and collection of cells under the nail plate that have not undergone desquamation), and splinter hemorrhage
 - Acrodermatitis continua of Hallopeau (ACH): rare pustular eruption on the distal portions of the fingers and less often, on the toes. Classified as a form of acropustular psoriasis that tends to be resistant to treatment
 - Histology mirrors that of psoriasis in the skin, except that hypergranulosis is more often a feature
12. Beau's lines (Fig. 3-15)
- Interruption of growth in the nail matrix will produce transverse linear depressions in the nail plate separated by areas of normal nail
 - Can be seen in the following conditions: chronic paronychia, chemotherapy, use of systemic retinoids, fever, illness, Raynaud's disease, pemphigus, trauma
13. Median canaliform dystrophy of Heller (Fig. 3-16)
- Midline split with backward-angled ridges ("fir tree")

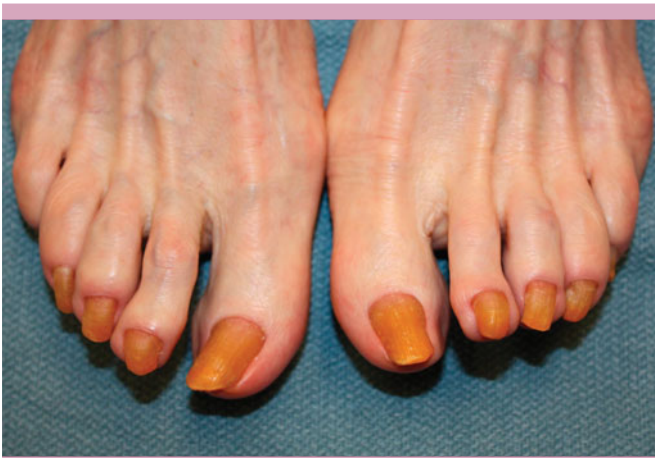


FIGURE 3-14 Yellow nails. (Courtesy of Dr. Ravi Ubriani.)



FIGURE 3-15 Beau's lines. (Courtesy of Dr. Sharon Hymes.)

- Beginning at or distal to the proximal nail fold
 - Etiology unknown, occasionally associated with prior local trauma or the initiation of treatment with isotretinoin
 - May be related to habit tic deformity
 - Enlarged lunula resulting from pressure on the base of the nail
14. Pterygium ("angel-wing" deformity)
- Has been described on both dorsal and ventral aspects of the nail plate
 - Dorsal nail plate: gradual progressive thinning of the nail plate and secondary fissuring caused by the fusion of the proximal nail fold to the matrix and then to the nail bed
 - Portions of the divided nail plate progressively decrease in size as the pterygium widens
 - Total loss of the nail with permanent atrophy
 - Associated with: lichen planus, bullous disorders, radiotherapy, digital ischemia, trauma, congenital
 - Ventral nail plate: distal extension of the hyponychial tissue that is anchored to the undersurface of the nail, thereby obliterating the distal groove. Also known as pterygium inversum unguis
 - Associated with: scleroderma, Raynaud's disease, median nerve causalgia (sympathetic maintained pain), formaldehyde/nail polish, trauma, congenital
15. Brachyonychia/racquet nail
- Short nails, the width of nail plate and nail bed is greater than length, occurs with a congenitally short distal phalanx
 - Thumb involvement is common, may be bilateral
 - Autosomal dominant trait secondary to obliteration of the epiphyseal line



FIGURE 3-16 Median canaliform dystrophy. (Courtesy of Dr. Ravi Ubriani.)

- Associated with: acroosteolysis, Down's syndrome, Rubenstein-Taybi syndrome, nail biting, bone resorption in hyperparathyroidism, or psoriatic arthropathy
16. Onychorrhexis
- Longitudinal nail ridging (aged nails)
 - Abnormalities in epidermal growth and keratinization of the proximal nail matrix
 - Associated with the following disorders: lichen planus, alopecia areata, rheumatoid arthritis, graft-versus-host disease, drugs: isotretinoin, thallium poisoning
17. Clubbing (Fig. 3-17)
- Increased transverse and longitudinal nail curvature
 - Hypertrophy of the soft tissue components of the digit's pulp
 - Hyperplasia of the fibrovascular tissue at the base of the nail
 - Early clubbing obliterates the normal diamond-shaped window formed at the base of the nail beds when there is opposition of the dorsum of two fingers from opposite hands. The angle that the proximal nail fold makes with the proximal nail plate is called Lovibond's angle. Normally this is about 160 degrees. In clubbing, it exceeds 180 degrees
 - Associated with: inflammatory bowel disease, pulmonary malignancy, asbestosis, chronic bronchitis, chronic obstructive pulmonary

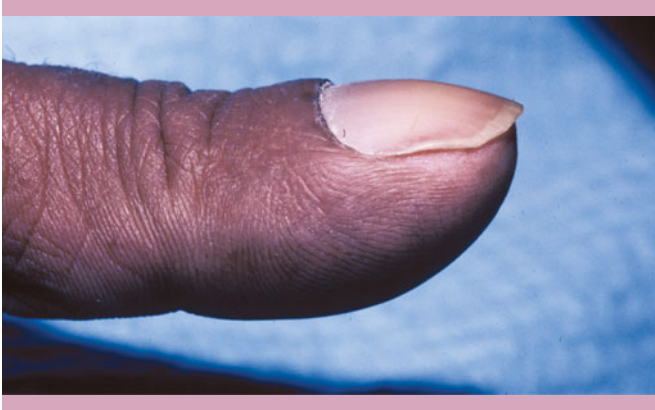


FIGURE 3-17 Clubbing. (Courtesy of Dr. Robert Jordon.)



FIGURE 3-18 Verruca. (Courtesy of Dr. Asra Ali.)

disease (COPD), cirrhosis, congenital heart disease, endocarditis, atrioventricular malformations, fistulas

18. Anonychia

- Absence of all or part of one or several nails
- May be congenital (with underlying bone abnormalities) or acquired (usually associated with lichen planus)
- Occurs sporadically or may have a dominant or recessive inheritance pattern

19. Acrokeratosis paraneoplastica (Bazex syndrome)

- Multiple, well-defined, psoriasiform, scaly, erythematous patches and plaques, distributed symmetrically over dorsa of hands and feet, helices of ears with similar lesions
- Palms and soles with keratoderma-like lesions
- Nail changes: ridging, thickening, yellow discoloration, onycholysis, paronychia
- Clinical course: acrokeratosis on the hands, feet, ears and nose that spreads progressively to the arms, legs and trunk as the tumor grows
- More than half of acrokeratosis paraneoplastica associated malignancies are found in the upper aerodigestive tract (upper parts of the respiratory and gastrointestinal tracts)
- Regional lymphadenopathy is often present
- In nearly two-thirds of cases, cutaneous lesions precede the symptoms or diagnosis of malignancy
- Cutaneous manifestations disappear during the treatment of the tumor

Tumors of the Nail Area

1. Periungual and subungual warts (Fig. 3-18)

- Hyperkeratotic papules with a rough surface: caused by human papilloma virus, most frequently types 1, 2, and 4

- Most common nail tumor that affect fingernails more often than toenails
- Direct trauma usually causes inoculation of the virus and initiates the localized viral infection, penetration of papilloma viruses into the skin is favored by skin abrasion or maceration
- Clinical development of warts occurs a few weeks to more than 1 year after inoculation
- Subungual warts may appear as a nodule under the nail plate and may result in onycholysis; it may present as a linear growth under the nail plate causing a longitudinal band of onycholysis with splinter hemorrhages
- Warts may produce slight matrix damage due to compression, resulting in nail plate ridging and grooving
- Periungual warts are asymptomatic, however, there may be pain associated with subungual warts
- Located around the nailfold, usually extend under the nail plate and may lie adjacent to the nail matrix
- Histology: hyperkeratosis with columns of parakeratosis overlying elongated papillae, hypergranulosis, and koilocytic changes
- Bowen's disease and squamous cell carcinoma have been reported to occur in long-standing periungual warts

2. Epidermal inclusion cyst

- Occur secondary to traumatic impregnation of the dermis with epidermal cells
- Cyst is lined with epidermis and filled with keratin
- Occasionally observed under the nail following trauma (such as a complication of nail surgery)
- Can erode adjacent structures, including bone
- Often asymptomatic, however, rupture of the cyst wall can elicit a foreign-body giant-cell reaction

- May appear as a subungual tumor raising the nail plate or causing a bulbous enlargement of the terminal phalanx
 - X-ray will show a sharply demarcated, round defect
 - Treatment by surgical removal of the cyst contents and the wall of the cyst
3. Onychomatricoma
- Uncommon benign tumor of the nail matrix
 - Longitudinal band of yellow thickening of the nail plate with longitudinal ridging
 - Increased transverse curvature of the nail, splinter hemorrhages of the proximal nail plate
 - Villous tumor projections in the nail plate, MRI shows tumoral core in the matrix area and invagination of the lesion into the funnel-shaped nail plate
 - Fibroepithelial tumor that consists of nail matrix epithelium over a connective tissue core
 - Epithelium may show clear cell change
 - Treatment
 - Simple retraction of the proximal nail fold allows superficial removal of the tumor from the matrix
4. Subungual and periungual keratoacanthoma
- May occur as solitary or multiple tumors
 - Rare, benign, rapidly growing, and locally aggressive
 - Usually situated below the edge of the nail plate or in the most distal portion of the nail bed
 - Lesion may start as a small and painful keratotic nodule visible beneath the free edge of the nail plate, occasionally it occurs under the proximal nail fold
 - Rapid growth to a 1- to 2-cm lesion within 4 to 8 weeks
 - The tumor can erode the bone, radiographically; it appears as a well-defined, crescent-shaped lytic defect (MRI is superior to radiographic studies in detecting an erosion of the distal phalanx)
 - Treatment: removal of the entire tumor with histologic control of the resection margins. The patient should be followed to rule out a recurrence
5. Acquired periungual fibrokeratoma
- Asymptomatic nodule with a hyperkeratotic tip, narrow base
 - Possibly caused by trauma
 - Variant of acquired digital fibrokeratoma
 - Emerges from beneath the proximal nail fold, grows on the nail and causes sharp longitudinal depressions
 - Some of these lesions originate from within the matrix and thus grow in the nail plate, eventually to emerge in the middle of the nail. (also called “dissecting ungual fibrokeratoma”)
- Histology demonstrates a hyperkeratotic and acanthotic epithelium with prominence of the granular layer overlying a dense and hypocellular collagenous tissue core
 - Immunohistochemistry shows that the fibroblasts are vimentin positive, and many of them stain with HHF35 (monoclonal antibody, specific for muscle actin)
 - Treatment: excision
6. Koenen’s tumor
- Periungual fibroma
 - Develops in about 50% of the cases of tuberous sclerosis (epiloia or Bournville-Pringle disease)
 - Usually appear between the ages of 12 and 14 years and increase progressively in size and number with age
 - Small, round, smooth, flesh-colored, asymptomatic, more frequent on toes than on fingers
 - Tumors grow out of the nail fold, overgrow the nail bed and destroy the nail plate. May cause longitudinal depressions in the nail plate
 - Sometimes tumors also grow in the nail plate
 - Histology: similar to that of fibrokeratoma as described above with atypical stellate myofibroblasts in the tissue core
 - Treatment: Excessively large tumors often are painful and should be excised at their base
7. Infantile digital fibromatosis
- (1- to 2-cm) Round, smooth, dome-shaped, shiny, firm red dermal nodules
 - Dorsal and axial surfaces of the fingers and toes
 - Not painful but can lead to functional deformity of a joint or cause limited mobility
 - It may be present at the time of birth or develop within the first year of life
 - Slow growth in the first month, followed by a rapid phase of growth (10–14 months), then be spontaneous involution
 - Conservative approach unless IDF causes a problem with mobility
 - Histology: scattered cells with eosinophilic cytoplasmic inclusions on routine hematoxylin and eosin staining. Inclusions are typically juxtanuclear and may even indent the adjacent nucleus
8. Bowen’s disease (in situ epidermoid carcinoma)
- Carcinoma in situ of the nail that differs from other variants. squamous cell carcinoma
 - Etiology linked to HPV-16, -34, and -35; arsenic also may play a role (also think about association with genital warts), exposure to x-ray
 - Presents as a circumscribed plaque with a warty surface extending from the nail groove both under

- and around the nail, periungual swelling due to deep tumor proliferation
 - Commonly presents with subungual involvement with extensive hyperkeratosis of the nail bed, associated with partial or total nail loss
 - Less common presentations: longitudinal melanonychia, lifting of the nail plate by subungual pseudofibrokeratoma
 - Nail dystrophy develops when the matrix is affected
 - Carcinoma cuniculatum: rare variant of squamous cell carcinoma with low biologic malignancy
 - Treatment: imiquimod, photodynamic therapy, methotrexate, radiation therapy, Mohs' micrographic surgery, excisional surgery, bone involvement requires amputation of the distal phalanx
9. Myxoid cyst (digital mucoid cyst) (Fig. 3-19)
- Asymptomatic, smooth nodule that enlarges slowly
 - Typically located at the distal interphalangeal (DIP) joints or in the proximal nail fold
 - A split or groove in the nail develops distally
 - Incision of the cyst results in extrusion of clear jelly-like material
10. Subungual exostosis and osteochondroma
- Subungual exostoses are not true tumors but rather are outgrowths of normal bone or calcified cartilaginous remains
- Location: commonly in the dorso-medial aspect of the tip of the great toe, although subungual exostoses may also occur in lesser toes or, less commonly, thumb, or index fingers
 - Triad of pain (the leading symptom), nail deformation, and radiographic features is usually diagnostic
 - Trauma is the main cause
 - Begin as small elevations on the dorsal aspect of the distal phalanx and may eventually emerge from under the nail edge or destroy the nail plate
11. Osteochondroma
- Bone-hard tumor, confirmed by x-ray
 - History of trauma, growth rate is slow
 - Radiographic studies show a well-defined, circumscribed, pedunculated or sessile bone growth projecting from the dorsum of the distal phalanx near the epiphyseal line
 - Therapy of subungual exostosis and osteochondroma consists of local curettage or excision
12. Giant cell tumor of the tendon sheath
- Solitary, often lobulated, slow-growing, skin colored, and smooth-surfaced nodule that tends to feel firm and rubbery
 - usually occurs on the dorsum of the distal interphalangeal joint, rarely it can present in the region of the lateral nail fold and may interfere with nail growth
 - Periodic inflammation and drainage may occur
 - Histopathology shows a cellular tumor composed of histiocytic and fibroblastic cells with a variable number of giant cells and some foam cells in a hyalin stroma with siderophages
 - Treatment is surgical excision



FIGURE 3-19 Myxoid cyst. (Courtesy of Dr. Ravi Ubriani.)

Vascular Tumors

1. Pyogenic granuloma
- Eruptive hemangioma usually seen following trauma
 - Small, benign, eruptive bluish/red nodule develops rapidly on the periungual skin, may develop distally in the hyponychium region or in the nail bed, especially associated with onycholysis of the toe
 - Tenderness and a tendency to bleed are characteristic features
 - Lesion becomes necrotic and forms a collarette of macerated white epithelium
 - Granulation tissue can be secondary to systemic retinoids, antiretroviral medications, cyclosporine, or epidermal growth factor receptor inhibitors. These medications can

all cause similar side effects in the nails: paronychia, xerosis, desquamation, and periungual granulation tissue

- Remove by excision at its base followed by electrodesiccation or application of Monsel's or aluminum chloride solution. CO₂ or pulsed dye lasers can also be used

2. Glomus tumor (Fig. 3-20)

- Triad: pain, tenderness, temperature sensitivity
- 75% of glomus tumors occur in the hand, especially in the fingertips and in particular in the subungual area. One percent to 2% of all hand tumors are glomus tumors
- Intense, often pulsating pain that may be spontaneous or provoked by the slightest trauma or changes in temperature
- Tumor is seen through the nail plate as a small bluish to reddish-blue spot several millimeters in diameter: longitudinal erythronychia with a distal fissured nail plate, usually in a single digit in middle-aged women
- One half of the tumors cause minor nail deformities, ridging and fissuring. About 50% cause a depression on the dorsal aspect of the distal phalangeal bone or possibly a cyst, visible on radiographic study
- Transillumination may help localize the tumor, MRI has the highest sensitivity to localize the tumor
- Histology: tumor with afferent arteriole and vascular channels lined with endothelium and surrounded by irregularly arranged cuboidal cells with round dark nuclei and pale cytoplasm; positive for vimentin, a 42-kD muscle actin (with HHF 35), a smooth muscle actin (CGA 7), and myosin
- Treatment: surgical removal, recurrences occur in 10% to 20% of cases



FIGURE 3-20 Glomus tumor. (Courtesy of Dr. Ravi Ubriani.)

Vitamins and Nail Disease

- There is circumstantial evidence that vitamin and mineral supplementation can be beneficial in nail disease. A review from August 2007 suggests that there is no role for vitamin or mineral supplementation in healthy nails. Clinical cases such as nail changes in hemodialysis, anorexia, bulimia, and genodermatoses provide the circumstantial evidence of the role of vitamins and minerals in nail health
 - Biotin: shown in multiple well-designed studies to be an effective treatment for brittle nail syndrome, but takes two to three months to have an effect
 - Vitamin E: case reports have shown success in yellow nail syndrome, but the supplementation was in conjunction with other treatments
 - Retinoids and Vitamin A: Deficiency can be associated with eggshell nails. Overdosage or systemic retinoid therapy can result in numerous nail problems, including acute paronychia, pyogenic granulomas, plate fragility and thinning, onychorrhexis, onychoschizia, onychomadesis, median canaliform dystrophy, transverse leukonychia, and a desquamative erythroderma with complete destruction of the nails. Topical retinoids are beneficial in nail psoriasis and can have a role in pachyonychia congenita
 - Vitamin D: Topical use is beneficial in nail psoriasis
 - Vitamin B12: Deficiency can result in hyperpigmentation of the nail
 - Calcium: severe deficiency can lead to a transverse leukonychia
 - Iron: deficiency can result in koilonychia, as in Plummer-Vinson syndrome. Supplementation can reduce brittleness of the nails, even when laboratory evaluation reveals no iron deficiency
 - Zinc: supplementation improves nail changes in acrodermatitis enteropathica. Acute onset deficiency can lead to a transverse leukonychia or Beau's lines
 - Selenium: Super-therapeutic selenium administration can lead to multiple nail problems, including brittle nails, transverse yellowish-white or red streaks, or longitudinal streaks
 - Silicon: supplementation has been shown to decrease nail brittleness in well-designed studies
- Claims have been made regarding benefits from gelatin, L-methionine, ceratin, collagen, panthothenic acid, salt, chromium, rhodanates, pyridoxine, vitamin C, or primrose oil, but the review did not find enough evidence to support a role for any of these supplements

Drug Reactions Affecting the Nails

- Many drug reactions can cause problems with the nails. Drug reactions in the nails can differ from

other cutaneous drug reactions because the kinetics of nail formation can result in delayed or prolonged abnormalities

- Teratogenesis: nail hypoplasia and anonychia may result from drugs taken during pregnancy. Anticonvulsants and anticoagulants are the most common causes
- Beau's lines and onychomadesis: result from acute severe toxicity to the nail matrix keratinization. Is clinically noted weeks after administration of the drug because of the slow growth of the nail. The most common causes are chemotherapy and radiation but these have been described with many different medications
- Nail fragility: chemotherapy, retinoids, antiretroviral agents
- Slowed nail growth: cyclosporine, heparin, lithium, methotrexate, and zidovudine
- Increased nail growth: fluconazole, itraconazole, levodopa, oral contraceptives
- Transverse leukonychia: results from retention of nuclei in the nail plate due to transient impairment of keratinization in the matrix. When they present as bands along the entire width of the nail plate, they are known as Mees' lines. This finding has been reported with many medications including chemotherapy, cyclosporine, and retinoids, and can be seen in arsenic or thallium poisoning. Apparent leukonychia that does not migrate with nail growth and fades with compression is called Muehrcke's lines. It is associated with low albumin and can be seen in patients treated with chemotherapy even with normal albumin levels
- Onycholysis and photo-onycholysis: Result from acute toxicity to the nail bed epithelium. Onycholysis with subungual abscess has been reported most frequently with taxane chemotherapy, but has also been reported with methotrexate, retinoids, and infliximab. Photo-onycholysis is seen with PUVA, tetracyclines, fluoroquinolones, OCPs, thiazide diuretics, and captopril
- Acute paronychia: can be seen with methotrexate, antiretrovirals (indinavir and lamivudine), retinoids (especially isotretinoin), and epidermal growth factor receptor inhibitors (gefitinib, erlotinib, and cetuximab)
- Pyogenic granulomas: causes are similar to acute paronychia. Can be caused by cyclosporine, indinavir, and epidermal growth factor receptor inhibitors
- Ischemic changes: Beta-blockers (especially propranolol) and bleomycin can produce ischemic and Raynaud's phenomenon. Bleomycin effects can be seen several months after treatment

- Subungual hemorrhages: antithrombotics, anticoagulants, taxanes, tetracyclines, and ganciclovir
- Nail atrophy: prolonged application of high-potency topical steroids
- Melanonychia: zidovudine, chemotherapy, hydroxyurea, psoralens all can cause activation of melanocytes and appearance of melanonychia. Radiation therapy can cause melanonychia even when used remote from the affected area
- Pigmentation: deposition of agents in the nails and subungual tissue can produce pigmentary changes. Tetracycline (yellow), gold salts (yellow), and clofazimine (dark-brown) deposit in the nails – these deposits will grow out with the nails and will be parallel to the lunula. Minocycline (blue-gray) and antimalarials (blue-brown) can deposit in the subungual tissues – these deposits will not grow out with nail growth. Tar and anthralin can stain the superficial layers of the nail plate and have a proximal border parallel to the cuticle as they are not dependent on endogenous deposition

QUIZ

Questions

1. A 56-year-old woman presents with a split nail on her left second finger. There is a bluish subungual discoloration proximal to the split. She complains of tenderness and temperature sensitivity in the affected digit. The most likely cause is:
 - A. Blue nevus
 - B. Glomus tumor
 - C. Myxoid cyst
 - D. Pyogenic granuloma
 - E. Squamous cell carcinoma
2. Epidermal growth factor receptor inhibitors can cause which of the following side effects?
 - A. Onycholysis
 - B. Paronychia
 - C. Yellow nails
 - D. Clubbing
 - E. Splinter hemorrhages
3. Pterygium inversum unguis is associated with which of the following diseases?
 - A. Psoriasis
 - B. Lichen planus
 - C. Scleroderma
 - D. Alopecia areata
 - E. Congestive heart failure

4. Which of the following disorders can result in loss of both the cuticle and lunula?
 - A. Chronic paronychia
 - B. Yellow-nail syndrome
 - C. Psoriasis
 - D. Rubenstein-Taybi syndrome
 - E. Alopecia areata
5. A 60-year-old man develops transverse white bands in all of his nails that blanch with pressure. The most appropriate initial test would be:
 - A. Arsenic level
 - B. Albumin
 - C. Liver function
 - D. Chest x-ray
 - E. Fasting glucose
6. What is the approximate growth rate of normal fingernails?
 - A. 0.1 mm/day
 - B. 0.2 mm/day
 - C. 0.3 mm/day
 - D. 0.4 mm/day
 - E. 0.5 mm/day
7. What medicine has the lowest rate of photo-induced onycholysis?
 - A. Demecycline
 - B. Doxycycline
 - C. Minocycline
 - D. Oxpsoralen
 - E. Tetracycline
8. A 40-year-old man has long-standing abnormalities of his fingernails. On exam, red and white longitudinal streaks with wedge-shaped distal nicking and subungual hyperkeratosis are noted. The most likely diagnosis is:
 - A. Anhidrotic ectodermal dysplasia
 - B. Dyskeratosis congenita
 - C. Keratosis follicularis
 - D. Pachydermoperiostosis
 - E. Pachyonychia congenita
9. A 5-year-old boy has congenital nail dystrophy with triangular lunulae in all his nails. He should be referred to which of the following clinical specialists?
 - A. Audiologist
 - B. Cardiologist
 - C. Dentist
 - D. Gastroenterologist
 - E. Nephrologist
10. Match the following nail findings with the most likely causative clinical scenario

<ol style="list-style-type: none"> i. Non-blanching transverse white bands that grow out with the nail ii. Blanchable paired transverse white bands that do not grow out with the nail iii. Opaque proximal nail with 1-2 mm distal pink band iv. Proximal pallor with brown/pink distal half of nail v. Increased transverse and longitudinal nail curvature with obliteration of Lovibond's angle 	<ol style="list-style-type: none"> A. Cirrhosis B. Renal failure C. Congestive heart failure D. Hypoalbuminemia E. Arsenic poisoning
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Answers

1. B (glomus tumor). The triad of glomus tumor is pain, tenderness, and temperature sensitivity. A single affected digit in a middle-aged woman is the correct demographic. A bluish subungual discoloration with a distal split is a typical appearance of a glomus tumor. While some of the other diagnoses could present with some of the symptoms, all three are distinctive for glomus tumor.
2. B (paronychia). Paronychia, periungual pyogenic granulomas, and xerosis are associated with epidermal growth factor receptor inhibitors.
3. C (scleroderma). Pterygium inversum unguis is associated with scleroderma and lupus. Dorsal pterygium is associated with lichen planus.
4. B (yellow-nail syndrome). Yellow-nail syndrome is associated with loss of both the cuticle and the lunula. Chronic paronychia can result in loss of the cuticle but not of the lunula. Rubenstein-Taybi syndrome is associated with broad thumbs.
5. B (albumin). The description is that of Muehrcke's nails. This is classically associated with low albumin. Arsenic level should be checked with Mees' lines, which do not blanch with pressure.
6. A (0.1 mm/day). Fingernails grow at 3 mm/month (0.1 mm/day) and take 5–6 months to regrow. Toenails grow at 1 mm/month (0.03 mm/day) and take 12–18 months to regrow.
7. C (minocycline). The rate of photo-onycholysis for tetracyclines is as follows: demecycline > doxycycline > tetracycline > minocycline.

8. C (keratosis follicularis). These nail changes are specific for Darier's disease, also known as keratosis follicularis.
 9. E (nephrologist). The clinical scenario describes nail-patella syndrome, also known as HOOD syndrome or Fong syndrome. This genodermatosis is associated with hypoplastic or absent patella, bilateral posterior iliac horns, radial head subluxation, scoliosis, palmoplantar hyperhidrosis, glomerulonephritis \pm renal failure, heterochromic irides, Lester iris, and cataract. Of the doctors listed, the nephrologist is the only suitable choice because of the risk of glomerulonephritis and renal failure.
 10. i-E; ii-D; iii-A; iv-B; v-C.
 - i. Non-blanching transverse white bands that grow out with the nail = Mees lines, classically associated with arsenic poisoning
 - ii. Blanchable paired transverse white bands that do not grow out with the nail = Muehrcke's nails, classically associated with hypoalbuminemia
 - iii. Opaque proximal nail with 1–2 mm distal pink band = Terry's nails, associated with cirrhosis
 - iv. Proximal pallor with brown/pink distal half of nail = Lindsay's nails or half-and-half nails, associated with renal failure
 - v. Increased transverse and longitudinal nail curvature with obliteration of Lovibond's angle = clubbing, associated with congestive heart failure
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ORAL PATHOLOGY

KAMAL BUSAIDY
ASRA ALI

BLACK HAIRY TONGUE (FIG. 4-1)

- Inadequate hygiene or microbial overgrowth stimulates elongation of filiform papillae (covers entire anterior dorsal tongue)
- Also associated with smoking, antibiotic therapy and poor general health status
- Clinical: black or brown hairlike projections on dorsal tongue
- Histology: elongation of filiform papillae; many microbial colonies between them
- Treatment: Eliminate smoking. Advise tongue brushing/scraping; aids in desquamation

ACTINIC CHEILOSIS/CHELITIS (FIG. 4-2)

- Due to long-term exposure to ultraviolet (UV) light (actinic radiation)
- Clinical findings
 - Thinned pale areas, especially lower lip. Later may develop areas of crusting
 - May progress to overt invasive squamous cell carcinoma
- Histology: hyperkeratosis usually is accompanied by dysplasia and superficial invasion
- Treatment: liquid nitrogen, imiquimod cream 5%, 5-fluorouracil, surgical excision

APHTHOUS STOMATITIS (FIG. 4-3)

- Clinical findings
 - One to several painful ulcers on the lining mucosa
 - Ulcers heal in 7 to 10 days without scarring
 - Recurrent aphthous ulcers (RAU)
 - Three clinical forms
 - RAU minor
 - ▲ Accounts for 80% of all RAUs
 - ▲ Discrete, painful, shallow, recurrent ulcers

- RAU major
 - ▲ Oval-shaped ulcers that are 1 to 3 cm in diameter
 - ▲ Severe form, 1 to 10 major aphthae may be present
- Herpetiform RAU: tends to occur in clusters that may consist of tens or hundreds of minute ulcers
- Causes difficult to pinpoint
 - Genetic
 - Vitamin deficiency: iron, folic acid, or vitamin B12
 - Immune dysregulation
 - Stress
 - Environmental factors
 - Local, chemical, or physical trauma (pathergy)
 - Contact allergy
 - HIV infection (associated with lesions)
 - Behçet syndrome (associated with lesions)
- Histology: non specific ulceration
- Treatment
 - Topical corticosteroids are the mainstay of treatment
 - Systemic agents
 - Systemic steroids for refractory cases
 - Colchicine (0.6 mg tid) if associated with arthralgias
 - Cimetidine (200 mg bid/qid)
 - Azathioprine (50 mg qd) if ocular lesions
 - Thalidomide

CICATRICAL PEMPHIGOID (FIG. 4-4)

- Clinical findings
 - Mucocutaneous vesiculobullous eruptions
 - Rupture leaving a slough covering a shallow ulcer that heals with scarring
 - Also may affect the eyes, mucous membranes of the genitalia and occasionally the skin



FIGURE 4-1 Black hairy tongue. (Courtesy of Dr. Nadarajah Vigneswaran.)



FIGURE 4-3 Aphthous stomatitis. (Courtesy of Dr. Nadarajah Vigneswaran.)



FIGURE 4-2 Actinic cheilosis. (Courtesy of Dr. Nadarajah Vigneswaran.)



FIGURE 4-4 Cicatricial pemphigoid. (Courtesy of Dr. Kamal Busaidy.)

- Bullous pemphigoid affects oral mucosa less than cicatricial form and is more self limiting, but otherwise histologically similar
- Histology: Subepidermal separation with eosinophilic infiltrate. Direct immunofluorescence of normal appearing mucosa shows immune deposits at the basement membrane
- Treatment: corticosteroid therapy: oral and/or topical; immunosuppressive therapy

SQUAMOUS CARCINOMA IN SITU (FIG. 4-5)

- Associated with tobacco use
- Can lead to invasive squamous cell carcinoma
- Clinical finding: white and/or red patch or soft ulcer
- Histology: anaplasia with or without hyperkeratosis; no invasion beyond basement membrane

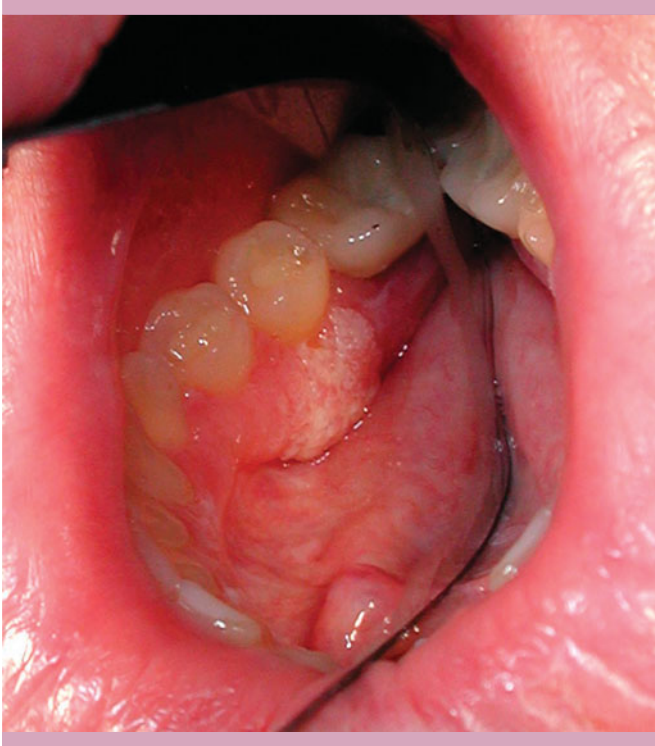


FIGURE 4-5 Carcinoma in situ. (Courtesy of Dr. Kamal Busaidy.)

- Treatment: Surgical excision. Close surveillance required due to potential for malignant transformation

FISSURED TONGUE (SCROTAL TONGUE, LINGUA PLICATA) (FIG. 4-6)

- Developmental etiology
- Seen in
 - Melkersson-Rosenthal's syndrome
 - Down's syndrome
- Frequently associated with benign migratory glossitis (geographic tongue)
- Clinical findings
 - Irregular clefts are observed in the dorsum tongue
 - Food debris and *Candida albicans* colonies may form in the fissures
 - May be associated with burning tongue
- Treatment: maintain good oral hygiene

FORDYCE'S SPOTS (FIG. 4-7)

- Clinical findings
 - Yellow papules



FIGURE 4-6 Fissured tongue. (Courtesy of Dr. Nadarajah Vigneswaran.)



FIGURE 4-7 Fordyce spots. (Courtesy of Dr. Nadarajah Vigneswaran.)

- Buccal mucosa (often bilateral), the vermillion upper lip
- Histology: ectopic sebaceous glands
- Treatment: none

FOCAL MELANOSIS (FIG. 4-8)

- Clinical findings: isolated macules, usually brown. Small (1–6mm diameter)
- Histology: increased melanin in basal layer. Otherwise normal appearance
- Treatment: none



FIGURE 4-8 Focal melanosis. (Courtesy of Dr. Mark Wong.)

MELANOACANTHOMA, MELANOACANTHOSIS (FIG. 4-9)

- Clinical findings: brown/black pigmentation of gingiva, tongue, palate. Macules can be several centimeters in diameter
- Histology: melanocytes scattered in epithelial layer. Acanthosis of epithelium
- Treatment: none

GEOGRAPHIC TONGUE (BENIGN MIGRATORY GLOSSITIS) (FIG. 4-10)

- Clinical findings
 - Atrophy of the filiform papillae of the tongue
 - Atrophic area surrounded by a serpiginous, white, hyperkeratotic border
 - Heals and develops again elsewhere (“migration”)
 - Burning sensation or an irritation of the tongue noted with hot or spicy foods
 - In patients with psoriasis, geographic tongue occurs in 10% of patients
- Histology: psoriasiform mucositis; elongation of the rete ridges is noted with associated hyperparakeratosis and acanthosis; absence of filiform papillae in center; clustering of neutrophils within the epithelium (Munro microabscesses)
- Treatment: none
- Prognosis: excellent; often self-limited

GRANULAR CELL TUMOR (GCT) (FIG. 4-11)

- Cells are of neural derivation (Schwann cells)

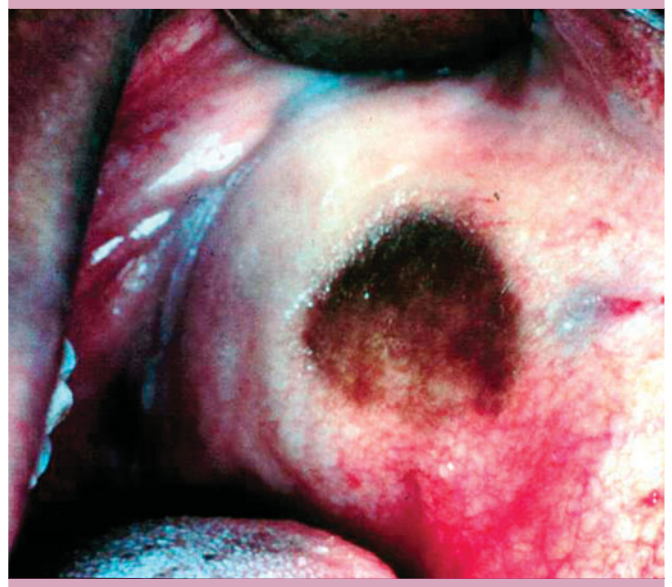


FIGURE 4-9 Melanoacanthoma. (Courtesy of Dr. Nadarajah Vigneswaran.)



FIGURE 4-10 Geographic tongue. (Courtesy of Dr. Nadarajah Vigneswaran.)

- Tongue is affected in approximately 25% of cases
- Gastrointestinal tract harbors approximately 5% of all GCTs
- Malignant GCTs are present if cells show cytologic features of malignancy
- Clinical findings: submucosal nodule covered with normal mucosa
- Histology
 - Tumor cells with abundant granular eosinophilic cytoplasm with centrally located vesicular or pyknotic nuclei and markedly enlarged lysosomes
 - Periodic acid–Schiff (PAS) staining; Sudan black B. trichrome preparations

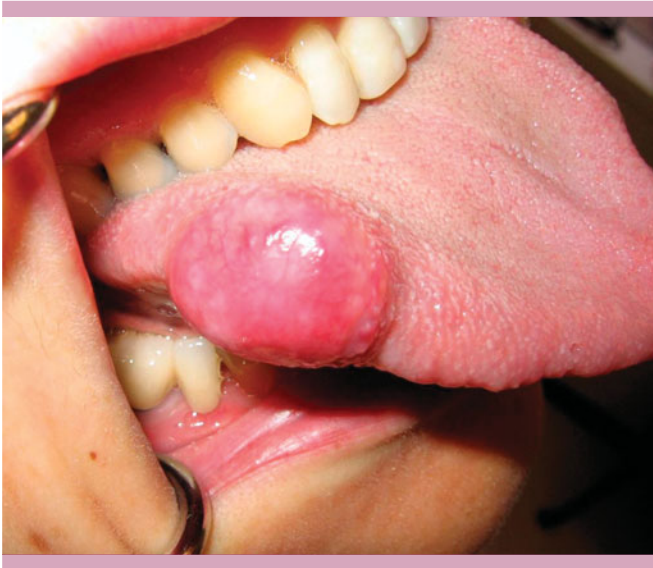


FIGURE 4-11 Granular cell tumor. (Courtesy of Dr. Mark Wong.)

- Immunohistochemical stains: S-100 protein, neuron-specific enolase, and NK1-C3, myelin-associated P0 and P2 proteins, myelin basic protein, and Leu-7
- Treatment: surgical excision
- Prognosis
 - Benign lesions; recurrence rates are 2% to 8%
 - Ki-67 immunoreactivity of 10% or more tumor cells is an adverse prognostic factor

ORAL LICHEN PLANUS (OLP) (FIGS. 4-12, 4-13)

- Clinical findings
 - Affects buccal, vestibular, lingual mucosa. 15% of patients with OLP have coincident skin lesions, (purple pruritic polygonal papules)
 - Reticular form: intersecting white lines in a netlike pattern; irregular white plaques (Wickham's striae)
 - Erosive form: ulceration and sloughing; potential for cancer formation (fewer than 1% of patients). Patients may have desquamative gingivitis in addition
 - OLP related to
 - Medications (Nonsteroidal anti-inflammatory drugs (NSAIDs), sulfonyleureas, antimalarials, beta-blockers, and some angiotensin-converting enzyme (ACE) inhibitors)
 - Dentures, amalgams; allergy to metals or components of dental appliances
 - Hepatic causes: hepatitis C virus (HCV) infection, autoimmune chronic active hepatitis, and primary biliary cirrhosis



FIGURE 4-12 Oral lichen planus – reticular type. (Courtesy of Dr. Bela Toth.)



FIGURE 4-13 Oral lichen planus – erosive type with desquamative gingivitis. (Courtesy of Dr. Kamal Busaidy.)

- Histology
 - Hyperkeratosis, parakeratosis, acanthosis, and sawtooth rete pegs
 - Chronic inflammation; bandlike subepithelial mononuclear infiltrate consisting of T cells and histiocytes
 - Basal cell liquefaction, degenerating basal keratinocytes that form colloid (Civatte, hyaline, cytoid) bodies
- Treatment
 - Eliminate factors that exacerbate soreness
 - Topical steroids, topical tacrolimus or cyclosporine

LYMPHANGIOMA (FIG. 4-14)

- Congenital malformation of the lymphatic system
- Clinical findings
 - Oral lesions: tongue, cheek most common sites
 - Small clusters of vesicles measuring about 2 to 4 mm
- Histology
 - Dilated lymph channels; papillary dermis expands
 - Channels lined by flat endothelial cells (stain positive for *Ulex europaeus* agglutinin-I)
- Treatment: surgical excision or produce scarring with chemicals or lasers

MEDIAN RHOMBOID GLOSSITIS (FIG. 4-15)

- Inflammatory lesion of the tongue secondary to candidiasis
- Clinical findings
 - Papillary atrophy on dorsal surface of the tongue along the midline, anterior to the foramen cecum
 - 1- to 3-cm rhomboid or oval, red, smooth
- Treatment: topical or systemic antifungal drugs

ODONTOGENIC KERATOCYST (OKC) (FIG. 4-16)

- Clinical findings
 - May be associated with nevoid basal cell carcinoma syndrome

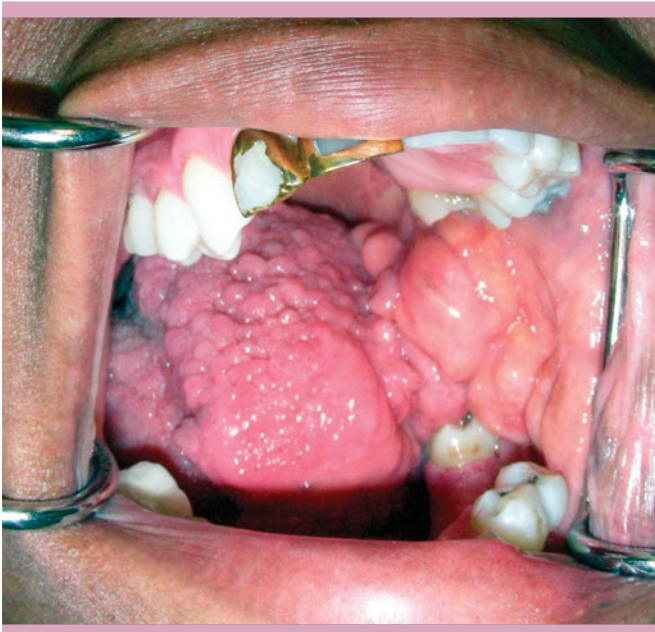


FIGURE 4-14 Lymphangioma. (Courtesy of Dr. Nagi Demian.)

- Benign
- 70% to 80% involve the mandible
- May grow to significant size before causing bony expansion or other symptoms
- Radiologic findings: Usually incidental finding on routine dental screening xrays. Well-demarcated radiolucency with a scalloped, radiopaque margin
- Histology
 - Cyst derived from the remnants of the dental lamina
 - Distinctive lining of 6 to 10 cells in thickness
 - Exhibits a basal cell layer of palisaded cells and a surface of corrugated parakeratin
- Treatment: enucleation versus resection



FIGURE 4-15 Median rhomboid glossitis. (Courtesy of Dr. Kamal Busaidy.)



FIGURE 4-16 Odontogenic keratocyst. (Courtesy of Dr. Kamal Busaidy.)

DRUG-INDUCED GINGIVAL HYPERPLASIA (FIG. 4-17)

- Clinical findings
 - Increase in the fibrous component of the gingiva
 - Long-term phenytoin (Dilantin), cyclosporine, and nifedipine
- Treatment
 - Good oral hygiene with regular dental cleanings
 - Discontinuation of precipitating drugs when possible
 - Surgical or laser resection of tissue for severe cases

XEROSTOMIA (DRY MOUTH)

- Clinical findings: dry, glossy atrophic mucosa
- Causes
 - Medications (secondary to anticholinergic effects): diuretics, sedatives, hypnotics, antihistamines, antihypertensives, antipsychotics, antidepressants, anticholinergics, and appetite suppressants
 - Radiation therapy to head and neck
 - Salivary gland surgery
 - Autoimmune disorders: human immunodeficiency virus (HIV) infections, systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome
 - Endocrine disorders: diabetes and hyperthyroidism
- Treatment
 - Discontinue offending medication
 - Commercial saliva substitute
 - Fluoride supplementation



FIGURE 4-17 Drug-induced gingival hyperplasia. (Courtesy of Dr. Mark Wong.)

LEUKOPLAKIA (LEUKOKERATOSIS, ERYTHROLEUKOPLAKIA) (FIG. 4-18)

- Clinical term describes mucosal conditions that produce a whiter than normal coloration of the mucous membranes
- Potentially precancerous especially if located in the floor of the mouth. Red patches have higher premalignant potential
- Clinical findings: White or red patch varies from flat, smooth, and slightly translucent macular areas to thick, firm, rough-surfaced, and fissured raised plaques
- Etiology: tobacco, alcohol, ultraviolet radiation, microorganisms, trauma
- Histology: thickened surface; keratin layer; a thickened spinous layer of chronic inflammatory cells in the connective tissue
- Treatment: Excision for small lesions. Close surveillance for malignant change

OSTEOMA (FIG. 4-19)

- Clinical findings
 - Usually solitary exophytic nodular growth of dense cortical bone on or within the mandible or maxilla
 - Multiple jaw osteomas may be associated with Gardner syndrome; autosomal dominant (gastrointestinal polyps, multiple osteomas,



FIGURE 4-18 Leukoplakia. (Courtesy of Dr. Bela Toth.)

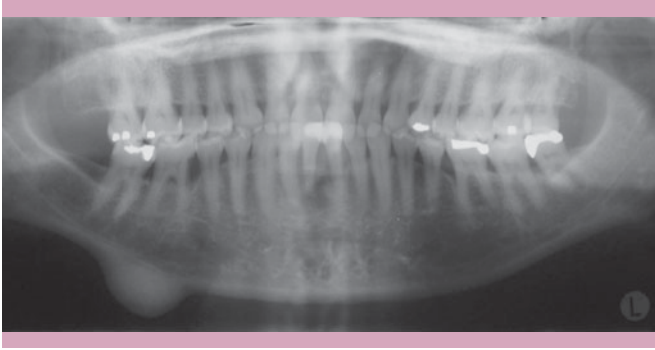


FIGURE 4-19 Osteoma. (Courtesy of Dr. Mark Wong.)

supernumerary teeth and epidermoid cysts/fibromas)

- Radiographic features: well-delineated or spherical calcifications
- Treatment: none. May require excision if severely deforming or interfere with function

KAPOSI'S SARCOMA

- Related to human herpes virus 8 and HIV
- Clinical findings
 - Hard palate with hyperpigmented macular lesions are most common and may include the gingiva, tongue, uvula, tonsils, pharynx, and trachea
 - Larger nodular lesions may become exophytic and ulcerated
- Histology
 - Spindle cells
 - Slit-like vascular spaces containing erythrocytes
 - Inflammatory cell infiltrate
- Treatment: excision. Systemic or intalesional chemotherapy

HUTCHINSON'S INCISORS (FIG. 4-20)

- Screwdriver-shaped central incisors seen in congenital syphilis

MULBERRY MOLARS

- Berry-like molars seen in congenital syphilis

LINEA ALBA (FIG. 4-21)

- Clinical findings
 - Linear white streak on the buccal mucosa at the occlusal line



FIGURE 4-20 Hutchinson's incisors. (Courtesy of Dr. Nadarajah Vigneswaran.)



FIGURE 4-21 Linea alba. (Courtesy of Dr. Kamal Busaidy.)

- Initiated by irritation from rough buccal cusps, bruxism, or habitual clenching of teeth
- Histology: parakeratosis of tissue
- Treatment: no treatment necessary

ORAL-FACIAL-DIGITAL SYNDROME TYPE I

- X-linked dominant
- Malformations of the face, oral cavity, and digits
- Clinical findings: oral anomalies: lobed tongue, hamartomas or lipomas of the tongue, cleft of the hard or soft palate, accessory gingival ferrule, hypodontia

PAPILLON-LEFÈVRE SYNDROME

- Autosomal recessive disorder
- Clinical findings
 - Aggressive periodontal disease. Palmar/plantar keratosis
 - Affects both primary and permanent dentitions
- Radiographic findings: Teeth appear to float in the soft tissue
- Treatment: periodontal therapy and antibiotics

PYOGENIC GRANULOMA (FIG. 4-22)

- Clinical findings
 - Smooth or lobulated red to purple masses that may be either pedunculated or sessile; commonly on the gingiva but can occur anywhere in the mouth
 - In response to chronic irritation (e.g., from rough surface of tooth)
- Histology: proliferating vascular channels and a mixed inflammatory infiltrate
- Treatment: surgical excision, laser excision. Removal of underlying irritant



FIGURE 4-22 Pyogenic granuloma. (Courtesy of Dr. Nadarajah Vigneswaran.)

SQUAMOUS CELL CARCINOMA (FIG. 4-23)

- Malignant neoplasm of stratified squamous epithelium
- Clinical findings
 - Early lesion: leukoplakias and erythroplakias
 - Late lesion: painless ulcer, tumorous mass, or verrucous (papillary growth)
 - Associated with tobacco smoking and alcohol use
- Histology
 - Keratin pearls (abnormal keratinization) invading lamina propria
 - Increased mitotic activity
 - Nuclear pleomorphism
 - Chronic inflammation
- Treatment: surgical excision, radiation therapy

VERRUCOUS CARCINOMA (FIG. 4-24)

- Papillary, superficial form of well-differentiated squamous cell carcinoma
- Rarely metastasizes
- Clinical findings: broad-based, exophytic, indurated lesion
- Histology: well-differentiated; basement membrane intact; marked epithelial hyperplasia and hyperparakeratosis
- Treatment: excision, radiation



FIGURE 4-23 Squamous cell carcinoma. (Courtesy of Dr. Bela Toth.)



FIGURE 4-24 Verrucous carcinoma. (Courtesy of Dr. Nadarajah Vigneswaran.)

AMALGAM TATTOO (FIG. 4-25)

- Clinical findings: bluish gray permanent area of pigmentation
- Histology: pigmented fragments of metal within the connective tissue
- Treatment: No treatment necessary

WHITE SPONGE NEVUS (FIG. 4-26)

- Autosomal dominant
- Defect of keratins 4 and 13
- Clinical findings



FIGURE 4-26 White sponge nevus. (Courtesy of Dr. Kelly Peters.)

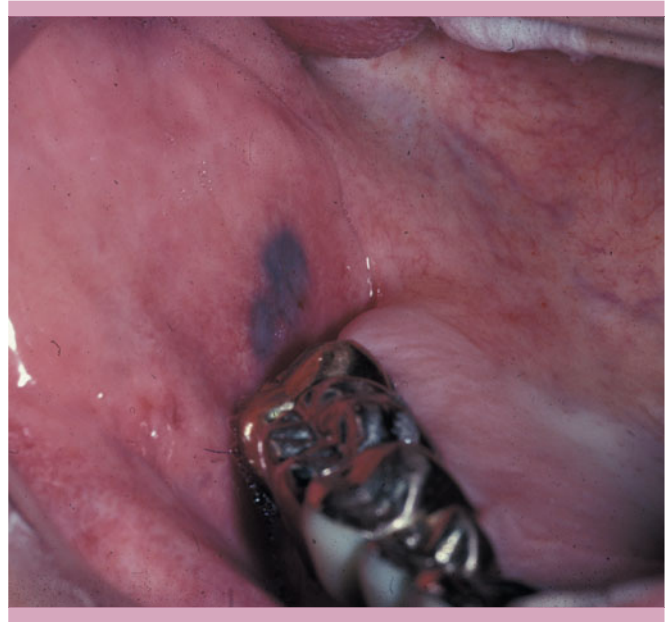


FIGURE 4-25 Amalgam tattoo. (Courtesy of Dr. Bela Toth.)

- Symmetric, thickened, white, corrugated or velvety, diffuse plaques
- Buccal mucosa, ventral tongue, labial mucosa, soft palate, alveolar mucosa, or floor of the mouth
- Histology: acanthosis, spongiosis, hyperkeratosis
- Treatment: No treatment is necessary

MUCOCELE (FIGS. 4-27, 4-28)

- Caused by traumatic injury to a minor salivary gland
- Clinical findings: dome shaped, soft, painless, translucent bluish lesion



FIGURE 4-27 Mucoccele. (Courtesy of Dr. Kamal Busaidy.)



FIGURE 4-28 Mucocoele – tongue. (Courtesy of Dr. Kamal Busaidy.)

- Most commonly on lower lip. Also occur on buccal mucosa, palate, tongue
- Histology: chronic inflammation with macrophages surrounding spilled saliva
- Treatment: surgical excision

TORI AND EXOSTOSES (FIGS. 4-29, 4-30)

- Overgrowth of mature bone
- Clinical findings
 - Elevated bony hard lesions extending out from the jaws
 - Tori are specifically in midline hard palate, or lingual of mandible
- Treatment: no treatment required unless interferes with denture wearing or oral hygiene; may be surgically removed

ORAL HAIRY LEUKOPLAKIA (FIG. 4-31)

- Secondary to Epstein-Barr virus (EBV)



FIGURE 4-29 Mandibular tori. (Courtesy of Dr. Bela Toth.)

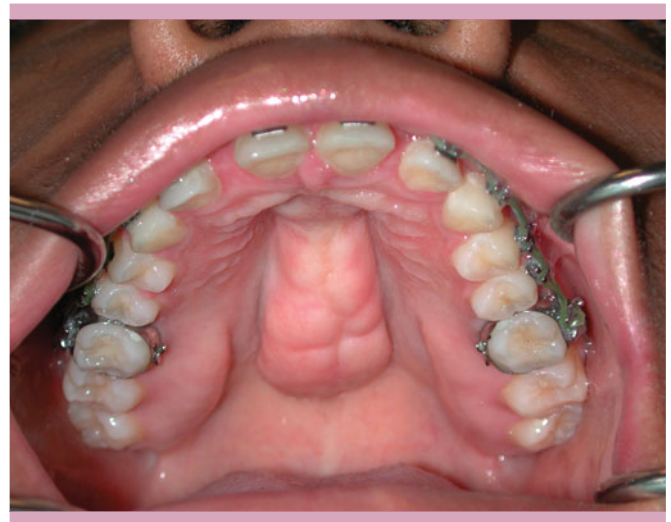


FIGURE 4-30 Palatal torus. (Courtesy of Dr. Kamal Busaidy.)

- Located mainly on the sides of the tongue
- Clinical findings
 - White thickening or coating of the lining of the mouth; does not scrape off
 - Typically affects immunosuppressed individuals
 - 40% of patients with HIV may develop this
- Treatment: No treatment typically required. May respond to acyclovir or ganciclovir, topical retinoids

ORAL CANDIDIASIS (THRUSH) (FIG. 4-32)

- Caused by *Candida albicans*



FIGURE 4-31 Oral hairy leukoplakia. (Courtesy of Dr. Bela Toth.)

- Clinical findings
 - Velvety white plaques in the mouth and on the tongue
 - Lesions may be rubbed off to leave behind an inflamed base that may be painful and may bleed
 - Usually a mild and self-limited illness
- Predisposing factors
 - Underlying immunodeficiency
 - Antibiotics, steroids
 - Dry mouth
 - Medication-induced: antidepressants, antipsychotics, chemotherapy, radiotherapy, or Sjögren's syndrome
 - Diabetes mellitus
 - Vitamin deficiency: iron, folate
- Treatment: oral antifungal agents

ACTINOMYCOSIS (FIG. 4-33)

- Facultatively or strictly anaerobic gram-positive bacilli
- Bacteria with fungi-like structures
- Normal flora of the upper respiratory, gastrointestinal and female genital tracts
- Causes opportunistic disease following disruption of mucosal barriers by trauma, surgery, or infection
- Clinical findings
 - Multiple abscesses and interconnecting sinus tracts: contain granules of microcolonies
 - Imbedded in tissue elements

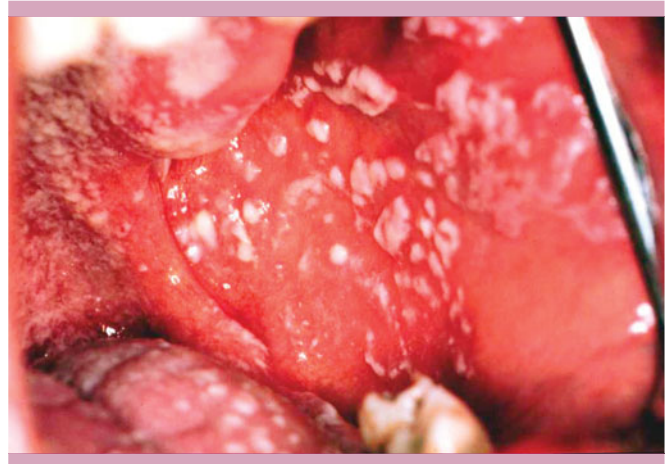


FIGURE 4-32 Oral candidiasis. (Courtesy of Dr. Nadarajah Vigneswaran.)



FIGURE 4-33 Actinomycosis. (Courtesy of Dr. Kamal Busaidy.)

- Macroscopic masses of filamentous bacterial cells that are “cemented” together by calcium phosphate
- Known as *sulfur granules* owing to their yellow or orange appearance
- Chronic suppuration results in granuloma formation and a fibrotic “walling off” of the lesion
- Cervicofacial actinomycosis

- Most common form
- Associated with poor oral hygiene, an invasive dental procedure, or oral trauma
- Tissue swelling with fibrosis and draining sinus tracts along the jawline
- Laboratory studies
 - Difficult to culture and identify because the numbers of organisms are limited in affected tissues and are sequestered in sulfur granules
 - Fastidious and slow growth (up to 2 weeks or more)
- Treatment
 - Surgical debridement
 - Long-term antibiotic therapy (susceptible to penicillin)
 - Maintain good oral hygiene
 - Prophylactic antibiotics prior to invasive oral or abdominal surgical procedures

CHEMOTHERAPY-INDUCED ORAL MUCOSITIS

- Clinical findings
 - Localized areas of full-thickness erosions occur
 - Can become covered by a fibrinous pseudomembrane
 - May become colonized by mixed flora
 - Dose-limiting toxicity for antimetabolites
 - Fluorouracil, methotrexate, and purine antagonists
 - Chemotherapeutic insult
 - Causes release of inflammatory cytokines, resulting in local tissue damage and increased vascularity
 - Decrease rates of cell division in the oral basal epithelium
 - Leads to reduced cell renewal, atrophy, and ulceration
- Treatment
 - Analgesics and nutritional support
 - Antimicrobial treatment for secondary infection
 - Tocopherol (vitamin E) accelerates mucosal healing
 - Ice chips
 - Induce local vasoconstriction; reduce amount of fluorouracil delivered to oral mucosal cells
 - Reduces the severity and duration of mucositis by 50%
 - Palifermin-synthetic keratinocyte growth factor

ANKYLOGLOSSIA (FIG. 4-34)

- Clinical findings: Attachment of the tongue to the floor of the mouth or anterior lingual gingivae limits tongue movement



FIGURE 4-34 Ankyloglossia. (Courtesy of Dr. Kamal Busaidy.)

- May be associated with speech defects or periodontal disease
- Treatment: surgical release of attachment

HEMANGIOMA (FIG. 4-35)

- Usually occurs in childhood
- Capillary type also known as strawberry hemangioma. Purple exophytic mass



FIGURE 4-35 Hemangioma. (Courtesy of Dr. Kamal Busaidy.)

- Cavernous type are deeper with larger blood filled spaces
- Treatment: Capillary type commonly involute in time. Cavernous type do not involute, and require excision if causing functional or cosmetic disturbances

CENTRAL GIANT CELL GRANULOMA (FIG. 4-36)

- Clinical findings
 - Painless expansion of alveolar bone
 - Most commonly in mandible; in 2nd to 4th decade
 - Displacement and loosening of teeth
 - Benign but may exhibit aggressive local growth
- Radiologic findings
 - Multilocular radiolucency. Radiographically indistinguishable from odontogenic keratocyst or ameloblastoma
- Histology: abundant multinucleated giant cells on background of mesenchymal cells
- Treatment: surgical excision. Intralesional steroids. Intralesional interferon. Systemic calcitonin

PERIPHERAL GIANT CELL GRANULOMA (FIG. 4-37)

- Clinical findings
 - Similar appearance to pyogenic granuloma
 - Location limited to gingivae
 - Commonly a response to local irritation or trauma
- Histology: Similar to central giant cell granuloma with multinucleated giant cells on a background of



FIGURE 4-37 Peripheral giant cell granuloma. (Courtesy of Dr. Kamal Busaidy.)

spindle shaped mesenchymal cells, and with occasional dystrophic calcifications

- Treatment: excision and removal of underlying irritant

ERYTHEMA MULTIFORME (FIG. 4-38)

- Associated with recent viral infection (herpes) or drugs (NSAIDs, sulphonamides, penicillamine)
- Clinical findings



FIGURE 4-36 Central giant cell granuloma. (Courtesy of Dr. Kamal Busaidy.)



FIGURE 4-38 Erythema multiforme. (Courtesy of Dr. Kamal Busaidy.)

- Shallow oral ulcerations, crusted bleeding lips, often erythematous skin lesions (“target lesions”)
- Steven-Johnson syndrome is more severe form of EM that also causes conjunctivitis and genital ulceration
- Histology: subepithelial edema and mixed inflammatory infiltrate
- Treatment: systemic corticosteroids; hydration; analgesia; self-limiting usually

NATAL TEETH (FIG. 4-39)

- Teeth are present at or around time of birth
- Usually mandibular incisors
- May exhibit significant mobility
- Treatment: removal if tooth mobility poses a risk of aspiration

BISPHOSPHONATE RELATED OSTEONECROSIS OF THE JAWS (FIG. 4-40)

- Clinical findings
 - Chronic exposure of bone in the mouth in a patient who has taken bisphosphonate drugs in the past
 - Often a history of recent dental extraction
 - Hypovascular, hypocellular, hypermineralized bone. Often superimposed bacterial colonization
- Treatment: conservative debridement. Oral hygiene. Antibiotics if superinfected



FIGURE 4-39 Natal teeth. (Courtesy of Dr. Kamal Busaidy.)

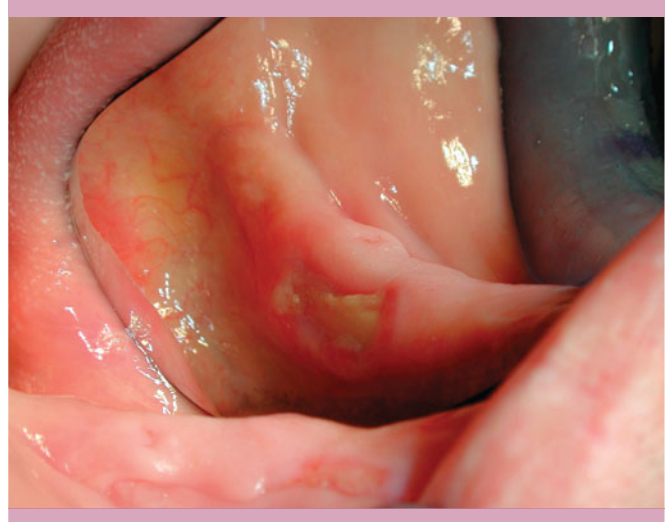


FIGURE 4-40 Bisphosphonate-related osteonecrosis of the jaws. (Courtesy of Dr. Kamal Busaidy.)

PERIPHERAL OSSIFYING FIBROMA (FIG. 4-41)

- Clinical findings
 - Firm, often ulcerated mass occurring exclusively on the gingivae. May look similar to pyogenic granuloma except for consistency
 - Commonly in the incisor region
 - May represent a pyogenic granuloma that has matured and become fibrosed/calcified
- Histology: fibrous proliferation with variable amounts of calcification
- Treatment: excision down to and including periosteum



FIGURE 4-41 Peripheral ossifying fibroma traumatic fibroma. (Courtesy of Dr. Kamal Busaidy.)

TRAUMATIC FIBROMA (FIG. 4-42)

- Clinical findings
 - Sessile or pedunculated, firm mass, most commonly on the buccal mucosa along occlusal line
 - Response to chronic trauma (e.g., cheek biting). Not true neoplasm
- Histology: dense mass of connective tissue covered by hyperkeratinized epithelium
- Treatment: excision

QUIZ**Questions**

1. A white lesion is present on the buccal mucosa. It cannot be rubbed off, and exhibits a lace-like pattern of striations. The striations do not disappear when the mucosa is stretched. The lesion most likely represents
 - A. Leukoedema
 - B. Leukoplakia
 - C. Lichen planus
 - D. Hairy leukoplakia
2. A 9-mm diameter purple soft ulcerated somewhat sessile mass is present on the marginal gingivae adjacent to the lower left incisor. It bleeds readily. Histologic examination reveals the presence of fibrous connective tissue, chronic mixed inflammatory infiltrate, and occasional areas of dystrophic calcification. The lesion most likely represents
 - A. Peripheral giant cell granuloma
 - B. Pyogenic granuloma
 - C. Peripheral ossifying fibroma
 - D. Epulis fissuratum
3. A 52-year-old patient with COPD and hypertension presents with diffuse gingival enlargement around all his teeth which has become progressively worse over the last year. He takes Singulair and verapamil. The most likely cause of the gingival condition is
 - A. Peripheral ossifying fibroma of the gingivae
 - B. Drug induced gingival hyperplasia
 - C. Hereditary gingival fibromatosis
 - D. Papillon-Lefèvre syndrome
4. Which of the following carries the most *unfavorable* prognosis?
 - A. 3-cm diameter verrucous carcinoma of the lip
 - B. 2-cm squamous cell carcinoma of the lateral tongue
 - C. 6-cm central giant cell granuloma of the mandible
 - D. 2-cm squamous cell carcinoma of the lower lip
5. Direct immunofluorescence demonstrates immune complex deposition along the basement membrane of a specimen of oral mucosa. The finding is most indicative of
 - A. Erythema multiforme
 - B. Reiter's syndrome
 - C. Pemphigus
 - D. Cicatricial pemphigoid
6. A 20-year-old male complains of soreness of his tongue. On examination the tongue exhibits two areas of erythema surrounded by a ragged whitish border, one on the left lateral surface, and the other on the tip of the tongue. The patient reports they arose within the last week and that a similar lesion had occurred on the right side of the tongue and healed spontaneously a month ago. The condition most likely represents
 - A. Erythroplakia
 - B. Geographic tongue
 - C. Median rhomboid glossitis
 - D. Lichen planus



FIGURE 4-42 Traumatic fibroma. (Courtesy of Dr. Kamal Busaidy.)

7. Black hairy tongue
 - A. Is a bacterial infection that should be treated with penicillin
 - B. Is the inevitable result of full thickness skin grafting to the tongue
 - C. Is a premalignant condition
 - D. Should be managed with periodic tongue brushing/scraping
8. Which of the following conditions may be seen in a patient with an accentuated linea alba?
 - A. Candidal infection of the mouth
 - B. Worn occlusal surfaces of teeth
 - C. Psoriatic skin lesions
 - D. Restricted mouth opening
9. A 25-year-old male with multiple jaw osteomas, epidermoid cysts and multiple supernumerary teeth should undergo which of the following:
 - A. CT examination of the head
 - B. Ultrasound examination of the abdomen
 - C. Colonoscopy
 - D. Blood test for parathyroid hormone level
10. Hypodontia is associated with which of the following?
 - A. Ectodermal dysplasia
 - B. Gardner's syndrome
 - C. Cleidocranial dysostosis
 - D. Down's syndrome

Answers

1. B. None of the lesions listed can be rubbed off. All appear white. Leukoedema appears grayish white, typically affecting the buccal mucosa bilaterally. There may be wrinkles or striations present, but these disappear when the mucosa is stretched. Leukoplakia does not typically have associated striations. Hairy leukoplakia appears as a shaggy white covering of the mucosa, typically on the lateral aspect of the tongue. The lace-like striae of the reticular form of lichen planus are termed Wickham's striae, and do not disappear with stretching of the mucosa either.
2. C. The first three lesions may appear remarkably similar on inspection, and may only be distinguishable histologically. Pyogenic granulomas are not restricted to the gingivae as are PGCG and POFs. Epulis fissuratum typically appears at the margin of an ill-fitting denture, and may be grooved by it. Histologically a PGCG demonstrates multinucleated giant cells. A POF demonstrates mineralized components that are not present in a pyogenic granuloma or an epulis fissuratum. The POF may in fact represent the mature form of a pyogenic granuloma that has undergone fibrosis and maturation.
3. B. Peripheral ossifying fibroma is a localized condition. Gingival fibromatosis may be idiopathic or hereditary. Hereditary gingival fibromatosis typically appears in the first two decades of life. Papillon-Lefèvre syndrome involves aggressive periodontal disease affecting both the deciduous and permanent dentitions, palmar/plantar keratoses and dry keratotic skin lesions, beginning within the first decade of life. Drugs associated with gingival hyperplasia include cyclosporine, phenytoin, and calcium channel blockers such as nifedipine, verapamil, diltiazem.
4. B. Verrucous carcinoma rarely metastasizes. Central giant cell granuloma can exhibit extremely aggressive local growth but does not metastasize. Squamous cell carcinoma metastasizes early. Lesions 2 cm in diameter on the tongue will have already invaded muscle, and therefore constitute T4 lesions. Squamous cell carcinoma lesions in the anterior part of the mouth and lips have a better prognosis than those in the posterior of the oral cavity.
5. D. Reiter's syndrome does not have any associated findings on direct immunofluorescence. Direct immunofluorescence of mucosa affected by erythema multiforme may demonstrate perivascular C3 deposits. Pemphigus demonstrates immune complex deposits on the intercellular surfaces within the epithelial layer. A finding of immune complex deposits along the basement membrane is characteristic of pemphigoid.
6. B. Erythroplakia is a red patch, often located within an area of leukoplakia, that does not resolve spontaneously, and is associated with a significant risk of progression to squamous cell carcinoma. Median rhomboid glossitis is an oval-shaped area of atrophy of surface papilla in the center of the dorsal surface of the tongue, and is usually asymptomatic. Lichen planus may present as smooth plaques on the tongue, and may come and go, giving a picture similar to erythema migrans (geographic tongue). However lesions of geographic tongue are typically well defined and bordered by a distinct irregular white line. The lesions heal spontaneously over a few weeks only to reappear in other areas of the tongue, hence giving the impression that they are migrating.
7. D. Overgrowth and subsequent staining of filiform papillae on the dorsal surface of the tongue results in black hairy tongue. While microbial deposits are common in the rough surface, treatment with antibiotics does not resolve the condition. The condition is not premalignant, and usually responds to good

oral hygiene measures, including periodic tongue brushing or scraping.

8. B. A linea alba is a common finding. It represents the region of friction on the buccal mucosa corresponding to the occlusal line of the teeth. However a markedly accentuated line may be seen in patients who habitually clench or grind their teeth. In such a circumstance there will commonly also be excessive wear of the teeth.
9. C. The findings are consistent with Gardner's syndrome. Intestinal polyps are extremely common in such patients, and colonoscopy is warranted to screen for malignancy since their rate of malignant transformation is so high.
10. A. Gardner's syndrome and cleidocranial dysostosis are associated with supernumerary teeth (extra teeth). Down's syndrome may be associated with cleft palate and macroglossia, but does not typically cause hypodontia. Ectodermal dysplasia affects multiple ectodermally derived elements, often resulting in

hypohidrosis, sparse hair and reduced number of teeth (hypodontia).

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GENITAL DERMATOLOGY

JENNIFER KREJCI-MANWARING
NISHATH ALI

LICHEN SCLEROSUS ET ATROPHICUS (LS) (FIG. 5-1)

- Atrophic white papules or plaques, most commonly affects the anogenital area in females (85% to 98% of patients) with extragenital involvement in 15% to 20%
- Figure-of-eight lesion when perineum and anus involved
- Females affected more often than males
- Secondary problems: candidiasis or atrophic vaginitis
- Severe cases can lead to scarring of vaginal vault and introitus with fusion of the labia minora and narrowing of the introitus, leading to a buried clitoris
- Penile LS (balanitis xerotica obliterans)
 - Common in middle age
 - Glans and inner aspect of the prepuce or circumferentially around the urethral meatus (can cause phimosis in uncircumcised males)
- Squamous cell carcinoma can arise in lesions in males and females
- Etiology is unknown: possible immune dysregulation with organ specific antibodies; infective agents have been linked with LS: pleiomorphic and, variably, acid fast bacilli and spirochetes
- Histology: orthokeratosis, hyperkeratosis, atrophy, basal cell layer vacuolation, edema and homogenization of collagen in the upper dermis; a focal perivascular or bandlike mononuclear cell infiltrate containing plasma cells is seen beneath the edema
- Treatment: high-potency topical glucocorticoids, topical antibiotics, circumcision for phimosis

PYRONIE'S DISEASE (PENILE FIBROMATOSIS)

- Idiopathic disorder
- Angulation of erect penis in middle age
- Caused by fibrosis of tunica albuginea, covers the corpora cavernosa

VULVODYNIA

- Diagnosis of exclusion
 - The cause has not yet been established; increased intraepithelial innervation in skin biopsies and an increase in the number of C-afferent nociceptors on special histopathological staining (S-100); an increase has also been found in the number of mast cells
- Vulvar discomfort, usually burning pain
 - International Society for the Study of Vulvovaginal Disease (ISSVD) classified the disease according to the localization of the pain in the vulva, whether it is generalized or localized and to whether it arises on provocation of the area or is unprovoked
- Q-tip test may localize pain
- Treatment: tricyclic antidepressant, topical corticosteroids/antifungals, gabapentin, biofeedback, low oxalate diet, oral calcium citrate, acupuncture, local botox injections

PEARLY PENILE PAPULES (FIG. 5-2)

- Normal variant
- Small pearly papules along the coronal rim; may extend to the frenulum and urethral meatus



FIGURE 5-1 Lichen sclerosus et atrophicus. (Courtesy of Dr. Libby Edwards.)

- Histology: angiofibromas with dense connective tissue and a rich vascular complex
- No treatment is indicated

SCROTAL CYSTS

- Common
- Diagnosis includes
 - Epidermal inclusion cyst
 - Steatocystoma simplex
 - Median raphe cyst lined with epithelium of combined epidermal and urothelial origin; congenital alterations in embryologic development, typically found on ventral penile shaft

SCROTAL CALCINOSIS

- May arise from dystrophic calcification of epidermal or follicular cysts
- Cysts with white chalky material seen after incision
- Treatment: surgical excision



FIGURE 5-2 Pearly penile papules. (Reprinted with permission from Wolff K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th ed. New York: McGraw-Hill; 2008.)

FOURNIER'S GANGRENE

- Necrotizing soft tissue infection of the genital and anorectal regions
- Tissue necrosis: cellulitis, fasciitis, and myositis
- Involves scrotum and penis with edema, erythema, skin necrosis, crepitus, and bulla formation
- Progression is rapid
- Etiologic factors: diabetes mellitus, periurethritis with urinary extravasation, indwelling catheter placement, traumatic injury
- Treatment: surgical debridement, prolonged antibiotics

DIAPER DERMATITIS (FIG. 5-3)

- Related to the irritant substances found in stool and superinfection with *Candida albicans*
- Presents with a bright red acute dermatitis confined to the genital and buttock areas with occasional extensions onto the abdomen or inner thighs and usually spares skin folds
- Treatment: barrier emollients, frequent diaper changes, topical antibacterial creams, topical antifungals

ANGIOKERATOMA OF FORDYCE (FIG. 5-4)

- Purple 1- to 5-mm papules
- Found on the scrotum, penis, and vulva
- Asymptomatic, occasionally bleed spontaneously or following trauma to or friction of skin
- Histology: dilated dermal blood vessels surrounded by a thin epidermis



FIGURE 5-3 Diaper dermatitis. (Courtesy of Dr. Libby Edwards.)

- Treatment: None needed; bleeding lesions can be ablated easily by electrocoagulation, laser

MALIGNANT CONDITIONS

Genital Bowen's Disease (GBD)/Erythroplasia of Queyrat (EQ)/Vulvar Intraepithelial Neoplasia

- Clinical presentations of high-grade penile intraepithelial neoplasia (PIN)
 - Most common etiologic factor: prevalence of human papilloma virus infection (HPV) in PIN is (60–100%)
 - HPV 16 is the most common type found
 - Other risk factors include: lack of circumcision, phimosis, balanitis, or any chronic inflammation of the penile skin
 - Progression into penile cancer is more common in EQ, occurring in around 30% of the cases
- Erythroplasia of Queyrat
 - Squamous cell carcinoma (SCC) in situ confined to the mucosa of the glans penis
 - One or more red, moist plaques on the mucosal surfaces of the glans, which may spread to the inner aspect of the prepuce
- Genital Bowen's disease
 - SCC in situ that presents as a single, scaly plaque, located on keratinized genital skin
 - Vulvar intraepithelial neoplasia (VIN) (Fig. 5-5) develops within a mature stratified squamous epithelium of vulvar epidermis or squamous mucosa
 - Classified from VIN I-III depending on depth in epithelium
 - HPV is consistently present in a high percentage of VIN
- Histology: full thickness dysplasia of the squamous epithelium. Epidermis and



FIGURE 5-4 Vulvar angiokeratomata. (Courtesy of Dr. Libby Edwards.)



FIGURE 5-5 Vulvar intraepithelial neoplasia III. (Courtesy of Dr. Libby Edwards.)

keratinocytes show disorderly maturation, parakeratosis and loss of granular layer with mitotic figures, multinucleated cells and dyskeratotic cells

- Prognosis: 3% to 10% of treated patients may develop invasive SCC of the vulva
- Treatment: electrosurgery, cryosurgery, radiation, laser surgery, topical application of 5-fluorouracil, as well as imiquimod 5% cream; Mohs' micrographic surgery

Bowenoid Papulosis

- Solitary or multiple, small, red, brown, or flesh colored papules with a flat or verrucous surface
- Occur on the shaft of the penis or the external genitalia of females
- Occurs in young sexually active adults
- Associated with HPV 16 or 18 most commonly
- Considered to be a distinct clinical variant of Bowen's disease that tends to run a benign course, (rate of transformation 2.9%)
- Histology: scattered dysplastic keratinocytes and mitotic figures, involvement of the acrosyringium with sparing of pilosebaceous structures
- Prognosis: local recurrences develop in 20% of patients, lesions can spontaneously regress, or can progress to invasive carcinoma
- Treatment: cryotherapy, electrodesiccation, laser, excision, or topical therapies: podophyllum, 5-fluorouracil, Imiquimod 5% cream, retinoic acid

Extramammary Paget's Disease (EMPD) (Fig. 5-6)

- Intraepithelial adenocarcinoma in situ with potential to become invasive
- Typically involves the following anatomical sites: vulvar, perianal, perineal, scrotal and penile regions (Paget cells are generally seen in apocrine gland-bearing skin)



FIGURE 5-6 Extramammary Paget's disease. (Courtesy of Dr. Libby Edwards.)

- Associated with cutaneous, adnexal-structure adenocarcinomas and with internal malignancies
- Occurs either as: *primary disease*—a primary intraepidermal neoplasm of the epidermis (apocrine adenocarcinoma in situ, derived from the Toker cells in apocrine glands) or *secondary disease*—less common, resulting from disease spread from an underlying internal malignancy (associated with adenocarcinoma arising in the rectum, cervix, ovary, or transitional cells)
- Eroded macular, slightly raised plaque with well-demarcated borders, pink, red, tan or brown, lesions can be pruritic
- Histology: epidermal acanthosis and elongated rete ridges. Paget's cells are large intraepidermal cells with a large nucleus and abundant pale cytoplasm
- Immunohistochemistry: cytokeratin 7, cytokeratin 20, gross cystic disease fluid protein
 - Cutaneous EMPD is characteristically positive for cytokeratin (CK)7, negative for CK20, and positive for gross cystic disease fluid protein (GCDFP)15+, whereas endodermal EMPD shows a CK7+ CK20+ GCDFP15- phenotype
- Treatment: surgery: wide surgical excision or Mohs' micrographic surgery

INFLAMMATORY CONDITIONS

Inverse Psoriasis (Fig. 5-7)

- Occurs in intertriginous areas
- Genital psoriasis is frequently accompanied by perianal and intergluteal cleft psoriasis
- Vulvar psoriasis affects fully keratinized skin, sparing the modified mucous membrane
- Dusky red, well-demarcated plaques; with moist, fine scale or a glazed, shiny surface texture
- Frequently complicated by *Candida* infection
- Treatment: hydrocortisone or other mild topical glucocorticoids, calcineurin inhibitors, calcipotriene

Lichen Planus (Fig. 5-8)

- Violaceous, flat-topped, polygonal papules with Wickham's striae (fine, whitish puncta or reticulated networks)
- Commonly affects oral mucosa, glans penis, wrists
- Severe scarring erosive variant more common in women
- Squamous cell carcinoma may occur in patients with genital lichen planus
- Associated with hepatitis C
- Histology: lichenoid infiltrate with basal cell vacuolarization, sawtooth rete ridges, Max-Joseph spaces
- Treatment: topical or intralesional steroids, calcineurin inhibitors



FIGURE 5-7 Inverse psoriasis. (Courtesy of Dr. Libby Edwards.)

Lichen Nitidus

- Small skin-colored papules with a glistening appearance
- Often on the penis, abdomen, and arms
- Histology: clawlike extension of rete ridges around a focal mixed dermal infiltrate
- Resolves spontaneously after months to years

Plasma Cell Balanitis (Balanitis Circumscripta Plasmacellularis, Zoon's Balanitis)

- Solitary, glistening, red or cayenne pepper-colored plaque on the glans penis and/or prepuce of uncircumcised men
- Female equivalent is plasma cell vulvitis (Fig. 5-9); oral mucosal equivalent is plasma cell orificial mucositis
- Histology: dense bandlike or lichenoid infiltrate with a predominance of plasma cells
- Treatment: low-potency topical steroids, circumcision, calcineurin inhibitors

Lichen Simplex Chronicus (Fig. 5-10)

- Scrotum and/or penis, vulva: symmetrical lichenified plaques



FIGURE 5-8 Lichen planus. (Courtesy of Dr. Libby Edwards.)



FIGURE 5-9 Plasma cell vulvitis. (Courtesy of Dr. Libby Edwards.)

- Results from chronic rubbing and scratching
- Areas of hypo- and hyperpigmentation may result
- Treatment: Castellani's paint, intralesional or topical mild- to moderate-strength glucocorticoid, and oral antipruritic agents

Hidradenitis Suppurativa (Fig. 5-11)

- Chronic, inflammatory, scarring disease of apocrine gland-bearing skin (axillae, buttocks, inguinal region, breasts)
- Follicular-occlusion triad: acne conglobata, hidradenitis suppurativa, dissecting cellulitis of the scalp



FIGURE 5-10 Lichen simplex chronicus. (Courtesy of Dr. Libby Edwards.)



FIGURE 5-11 Hidradinitis suppurativa. (Courtesy of Dr. Libby Edwards.)

- Early lesion is a tender dermal abscess; recurrent episodes cause scarring and sinus tract formation
- Rectal, urethral, and vaginal fistulas may develop rarely
- Staging
 - Stage I: solitary or multiple isolated abscess formation without scarring or sinus tracts
 - Stage II: recurrent abscesses, single or multiple widely separated lesions with sinus tract formation and cicatrization
 - Stage III: diffuse or broad involvement across a regional area with multiple interconnected sinus tracts and abscesses
- *Staphylococcus*, *Streptococcus*, and *E. coli* are most commonly cultured
- Histology: follicular plugging with various degrees of inflammation and fibrosis, dermal abscess
- Treatment: intralesional steroids, antibiotics, incision and drainage, isotretinoin; wide local excision may be performed in recalcitrant cases, liposuction with gland removal



FIGURE 5-12 Fixed drug eruption. (Courtesy of Dr. Libby Edwards.)

Fixed Drug Eruption (Fig. 5-12)

- Follows ingestion of a sensitizing hapten: barbiturates, carbamazepine, dapsone, griseofulvin, nonsteroidal anti-inflammatory drugs, phenazones, sulfonamides, tetracycline, Oxyphenbutazone was also reported as a frequent causative drug of mucosal fixed drug eruption
- Sharply demarcated, dusky, erythematous macules or erosions
- Heals with postinflammatory hyperpigmentation
- Recurs in the same location with rechallenge

- Common on glans and distal shaft of the penis, vulva, labia
- Other presentations:
 - Generalized or multiple fixed drug eruptions: multiple to numerous and are disseminated, shows polysensitivity, in which there is more than one causative drug and the drugs may be chemically unrelated
 - Erythema multiforme-like fixed drug eruptions: clinical manifestations are similar to those of erythema multiforme
 - Bullous fixed drug eruptions: subepidermal bullae, heal without scarring

- Treatment: fixed eruption heals in 2 to 3 weeks, drugs should be discontinued, desensitization can be tried, if necessary

Kawasaki's Disease (Mucocutaneous Lymph Node Syndrome)

- Thought to be mediated by bacterial toxins but etiology still elusive
- 80% of cases occur before 4 years of age
- Perineal erythema may be presenting feature
- Strawberry tongue, fissured lips, fever, cervical lymphadenopathy, non-purulent conjunctivitis, erythema/edema of hands and feet. Later, desquamation
- Risk for coronary artery aneurysm. Mortality approximately 1% in the United States
- Treatment: high dose aspirin, IVIg

Langerhan's Cell Histiocytosis (Histiocytosis X)

- Classified clinically into 4 types
 - *Lettere-Siwe disease*: acute diffuse form with visceral and bone lesions
 - *Hand-Schuller-Christian disease*: classic triad of diabetes insipidus, bone lesions, exophthalmos, chronic progressive course
 - *Eosinophilis granuloma*: localized variant with solitary bone lesions
 - *Congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker disease)*: benign variant with single or widespread lesions that spontaneously resolves
- Acute variant onset < 2 years of age. Other variants: onset in early childhood
- Non-healing groin rash common: papules, pustules, vesicles become crusted and impetiginized. Often confused with diaper dermatitis or seborrheic dermatitis
- Treatment: dependent on number of body systems involved but may include: chemotherapy, radiation or curettage (bone), topical corticosteroids, antibacterial agents, PUVA, nitrogen mustard (skin)

INHERITED DISEASES

Cystic Fibrosis

- Autosomal recessive
- Exocrine glands affected: involves the tracheobronchial tree, pancreas, and gastrointestinal tract
- Mucous plugs may cause fecal impaction, intussusception, and rectal prolapse in infancy
- Pancreatic insufficiency
- Progressive lung disease with chronic bronchitis, emphysema, and cor pulmonale
- Cutaneous features: increased amounts of electrolytes in the sweat lead to excessive skin wrinkling when the palms and soles are immersed in water

- It can present with a groin rash similar to acrodermatitis enteropathica

Acrodermatitis Enteropathica

- Autosomal recessive
- Inability to absorb sufficient zinc from the diet
- Triad: acral dermatitis, alopecia, and diarrhea
- Distribution: face, hands, feet, anogenital area
- Dry, scaly, eczematous plaques, perleche
- Progresses to vesicobullous, pustular, and erosive lesions
- Alopecia worsens with time
- Diarrhea is variable: intermittent or totally absent
- Treatment: supplementation with zinc salts

Hailey-Hailey (Familial Benign Pemphigus) (Fig. 5-13)

- Autosomal dominant, chromosome 3q
- Axillae, groin, intertriginous areas; mucosal surfaces are rarely involved
- Flaccid vesicles and blisters on an erythematous background
- Friction breaks blisters, resulting in erosions
- Frequent exacerbations, precipitated by friction and infection
- Histology: suprabasal cleavage, acantholysis, and intercellular edema ("dilapidated brick wall")
- Treatment: tetracyclines, fusidic acid, imidazoles, topical or systemic glucocorticoids

INFECTIONS AND INFESTATIONS

Candidiasis

- Usually caused by *C. albicans*
- Vaginal and vulvovaginal candidiasis



FIGURE 5-13 Hailey-Hailey disease. (Courtesy of Dr. Libby Edwards.)

- Thick vaginal discharge associated with burning, itching, and dysuria
- Whitish plaques on the vaginal wall with underlying erythema and surrounding edema; can extend to labia and perineum
- Balanitis or balanoposthitis
 - Small papules on glans or coronal sulcus
 - Erythematous erosions with a collerette of whitish scale
 - Infection may spread to the scrotum and inguinal areas
 - Confluent and discrete erythematous areas with pustular and erosive satellite lesions
- Treatment: oral or topical azoles

Crab Louse (*Pediculosis Pubis*)

- Parasite *Phthirus pubis*, the pubic louse
- Transmitted sexually; mites cling to pubic and facial hair/eyelashes
- Nits (egg casings) of head and crab lice are firmly cemented to the hairs of the host
- Main symptom is pruritus; bites are painless, rarely detected
- Maculae ceruleae: blue macules
- Treatment
 - Permethrin 1% cream rinse
 - Lindane 1% shampoo (potential for central nervous system toxicity; not recommended for use on infants, young children, or pregnant or nursing women)
 - Sexual contacts should be treated simultaneously

Tinea Cruris

- Dermatophytosis involving the groin area
- Causative dermatophytes: *Epidermophyton floccosum*, *Trichophyton rubrum*
- Dermatophytoses elsewhere on the body provide a reservoir for autoinfection in tinea cruris
- Clinical: multiple, erythematous papulovesicles with a well-margined, raised border
- Scrotum usually appears completely normal (*Candida* may spread to the scrotum)
- Treatment: decrease occlusion and moisture in the involved area; tolinaftate, and topical imidazoles, powder or minimally occlusive cream base

Erythrasma

- Pigmented or erythematous patches, can have fine scale
- Inguinal folds
- Coral red fluorescence under Wood's lamp due to coproporphyrin III
- Caused by *Corynebacterium minutissimum*
- Treated with topical erythromycin or clindamycin

Peri-anal Streptococcus Disease

- Group A – hemolytic streptococcus
- Sharply demarcated bright erythema or crusting in perianal area
- Usually children under 4 years of age
- May have constipation because of pain with defecation
- Associated with guttate psoriasis. Oral and rectal swabs for bacterial culture in children with outbreak
- Treatment: penicillin or erythromycin

BULLOUS DISEASES CAUSING GENITAL ULCERATION (COVERED IN OTHER CHAPTERS)

- Bullous pemphigoid
- Cicatricial pemphigus
- Linear IgA bullous dermatosis
- Pemphigus vulgaris
- Erythema multiforme
- Stevens-Johnson syndrome
- Behçet's syndrome

SEXUALLY TRANSMITTED DISEASES (DESCRIBED IN OTHER CHAPTERS)

- Bacterial vaginosis
- Chancroid
- Gonorrhea
- Granuloma inguinale
- Human immunodeficiency virus infection
- Syphilis
- Donovanosis
- Lymphogranuloma venereum
- Genital herpes
- Molluscum contagiosum
- Nongonococcal urethritis
- Pubic lice
- Trichomoniasis
- Human papilloma virus infection

QUIZ

Questions

1. A mother brings her 3-month-old infant to your office for evaluation of a rash in the diaper area. On exam there is erythema on the vulva and peri-anal area with sparing of the skin folds. What is the most likely cause?
 - A. Psoriasis
 - B. Zinc deficiency
 - C. Strep pyogenes
 - D. Irritation from urine and stool

2. A 55-year-old female with lichen sclerosis of the vagina and perineum has been well-controlled with topical clobetasol propionate ointment intermittently for the last 10 years. She now complains of an area that has increased pain, erythema, occasionally bleeds and does not heal. What are you worried about?
 - A. Squamous cell carcinoma
 - B. Atrophy from topical corticosteroids
 - C. Herpes genitalis
 - D. Contact dermatitis to clobetasol
3. A 40-year-old man presents with multiple, small, red-brown papules with a flat-to-verrucous surface on the shaft of his penis. The most common HPV serotype for this presentation is:
 - A. 6, 11
 - B. 7
 - C. 13
 - D. 16, 18
4. A 25-year-old medical student comes to your office because he notes an area of hyperpigmentation on the glans penis. The lesion will start out more erythematous but seems to wax and wane and at times is almost completely resolved. He is otherwise healthy except for seasonal allergies for which he takes an over-the-counter medicine to treat as needed. What do you suspect?
 - A. Recurrent herpes genitalis
 - B. Fixed drug reaction
 - C. Lichen planus
 - D. Zoon's balanitis
5. A 17-year-old female presents to your office with a new pruritic rash involving her axillae, inguinal area, and posterior neck. It is scaly and erythematous with crusting. Her father has a similar rash. What do you expect to see on histology?
 - A. Suprabasal cleavage, acantholysis, and serum scale crust
 - B. A lichenoid infiltrate in a band-like distribution which obscures the dermoepidermal junction
 - C. Parakeratosis and increased granular layer
 - D. Atypical cells with pale-staining cytoplasm and atypical nuclei, mitoses distributed singly or in clusters in the epithelium
6. Erythrasma is caused by:
 - A. *Kytococcus sedentarius*
 - B. *Corynebacterium tenuis*
 - C. *Corynebacterium minutissimus*
 - D. *Pseudomonas*
7. What is the best treatment for pubis pediculosis?
 - A. Malathion
 - B. Lindane
 - C. Permethrin
 - D. Shaving the pubic hair
8. You are called as a consult on an 8-month-old female who has a diaper rash that is unresponsive to treatment with topical antifungals and emollients. On biopsy you see large mononuclear cells with reniform nuclei scattered in the dermis. You expect what immunohistochemical stain to be positive?
 - A. CD7
 - B. CD1a
 - C. CD30
 - D. CD56
9. A 3-year-old child presents to the ER with fever, conjunctivitis, swelling of the hands and feet and peri-anal erythema. You recommend treatment with:
 - A. Low-dose aspirin
 - B. High-dose aspirin
 - C. Prednisone
 - D. High-dose aspirin and IVIg
10. A 29-year-old man complains of small blue/violet papules on his scrotum. He sometimes notices blood on his underwear that he attributes to scratching these lesions. They are otherwise asymptomatic and he has no medical problems. What is your next step?
 - A. Biopsy
 - B. Check HIV
 - C. Check alpha-galactosidase levels
 - D. Reassurance

Answers

1. C. This is a description of diaper dermatitis caused by the urine and stool in areas of contact. Psoriasis and peri-anal strep will also cause erythema in this area but does not have the classic sparing of the skin folds. Zinc deficiency is found in infants fed cow's milk or in acrodermatitis enteropathica once they are weaned from breast milk.
2. A. Squamous cell carcinoma is a rare complication of long-standing LS. Any area that becomes eroded, bleeds, and does not heal warrants a biopsy. Long-term use of topical super-potent steroids could lead to atrophy and cause skin breakdown but the question stated she used them intermittently.

3. D. This is a description of bowenoid papulosis, which is caused most commonly by HPV types 16 and 18. It is considered malignant but has a low rate of transformation (2.9%). Types 6 and 11 are responsible for most genital warts. Type 7 causes butcher's warts. Type 13 is associated with Heck's disease (focal epithelial hyperplasia).
4. B. This is a typical scenario for a fixed drug reaction related to pseudoephedrine, a common ingredient in cold and allergy medicine. HSV would have vesicles but could wax and wane with frequent recurrences. Lichen planus may be on the genitals in both the papular and erosive form but does not wax and wane. Zoon's balanitis also tends to be persistent unless treated and typically presents as a glistening patch on the glans in an uncircumcised male.
5. A. This is Hailey-Hailey. It is autosomal dominant and on pathology is described as the "dilapidated brick wall." Choice B refers to lichen planus. Choice C refers to axillary granular parakeratosis. Choice D refers to Paget's disease.
6. C. Erythrasma is caused by *Corynebacterium minutissimum*. *C. tenuis* causes trichomycosis axillaris. *Kytococcus* (formerly *Micrococcus*) sedentarius causes pitted keratolysis.
7. C. Pubic lice is best treated with permethrin cream (1% Nix® or 5% Elimite®). Shaving is the treatment of choice for trichomycosis axillaris which can affect the pubic hair.
8. B. This is Langerhan's cell histiocytosis. Langerhan's cells stain with S-100 and CD1a. CD7 stains T-cells and is sometimes lost in MF. CD30 is positive in lymphomatoid papulosis. CD56 is found in NK cell lymphoma.
9. D. This is Kawasaki's disease. Initial treatment includes high dose aspirin (80–100 mg/kg/d PO divided qid for 2 wk initial) plus IVIg.
10. D. This is angiokeratoma of Fordyce. It is a benign condition and you can reassure the patient. Fabry's disease has low levels of alpha-galactosidase but is associated with angiokeratoma corporis diffusum. Kaposi's could look similar clinically but typically are larger and more nodular. This would be a reason to check HIV.

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CONTACT DERMATITIS

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CONTACT DERMATITIS

- Inflammatory response of the skin to an antigen or irritant
- Allergic contact dermatitis (ACD)
 - Delayed type hypersensitivity reaction (type IV)
 - Langerhans' cells play a central role in processing and presenting antigen complexes
 - Individuals previously sensitized to the allergen will develop lesions. Subsequent exposure to the allergen will result in incrementally more severe reactions
 - Common allergens include: plants from the *Toxicodendron* genus (e.g., poison ivy), nickel sulfate, formaldehyde
 - Acute ACD: lesions appear within 24 to 96 hours of exposure to the allergen
- Irritant contact dermatitis (ICD)
 - Irritants produce various effects: cytotoxicity of the keratinocyte, disruption of lipid architecture, initiation of immunologic cascade
 - ICD will only occur in areas of the skin that has been in direct contact with the offending agent
 - Subsequent inflammatory response in the dermis
 - Caused mostly by chemicals
 - Two types
 - Mild irritants: require prolonged or repeated exposure before inflammation is noted
 - Strong irritants: strong acids, alkalis, can produce immediate reactions similar to thermal burns
- Clinical changes
 - Acute contact dermatitis: clear fluid-filled vesicles or bullae that appear on bright red edematous skin, pruritic

- Subacute contact dermatitis: less edema and formation of papules, pruritic
- Chronic contact dermatitis: minimal edema, scaling, skin fissuring, and lichenification
- Histology
 - Dermis with perivascular lymphocytes and other mononuclear cells, epidermal spongiosis, cytotoxicity more commonly seen in irritant contact dermatitis
 - Chronic ACD: acanthosis with hyperkeratosis and parakeratosis
 - Difficult to distinguish, clinically and histologically, allergic contact from irritant contact dermatitis

CONTACT URTICARIA

- An immunoglobulin E (IgE)-mediated immediate hypersensitivity reaction (type I)
- Immediate release of inflammatory mediators, resulting in a wheal-and-flare reaction
- Rubber latex currently is the most important source of allergic contact urticaria

PHOTOSENSITIVITY INDUCED BY EXOGENOUS AGENTS

- Photodermatitis
 - Diagnosed by the presence of lesions limited to sun-exposed body areas; certain substances transform into allergens (photoallergic) or irritants (phototoxic) by ultraviolet light
- Photoallergic reaction
 - Delayed-type hypersensitivity reaction (type IV)

- Onset delayed as long as 24 to 72 hours after exposure to the drug and light
 - Amount of drug required to elicit photoallergic reactions is considerably smaller than that required for phototoxic reaction
 - Irradiation of certain substances by ultraviolet light results in the transformation of the substance into allergens
 - Reactions resemble allergic contact dermatitis, with a distribution limited to sun-exposed areas of the body (see above)
 - Usually spares the lower eyelids, and the post-auricular and submental areas
 - When the reactions are severe or prolonged, they may extend into covered areas of skin
 - Examples of agents that can cause a photoallergic reaction (Tables 6-1 and 6-2)
 - Phototoxic reaction (Tables 6-3 and 6-4)
 - Often occur within minutes or hours of light exposure
 - Chemically induced nonimmunologic acute skin irritation
 - Does not require prior sensitization
 - Active chemical may enter the skin via topical administration or via ingestion, inhalation, or parenteral administration
 - Damaging effects of light-activated compounds on cell membranes
 - Most compounds are activated by wavelengths within the ultraviolet A (UV-A) (320–400 nm) range
 - Clinical appearance: an exaggerated sunburn reaction
 - Photopatch test
 - Used to find causative agent of photoallergic reaction
 - Photopatch testing protocol
 - Day 1: Determine minimal erythema doses (MEDs), and apply two sets of patches
 - Day 2: Read MEDs
 - Day 2: Remove patches, read, and irradiate one set (10 J/cm² UV-A)
 - Day 4: First reading
 - Days 5–9: Second reading
 - Polymers of coniferyl alcohol with benzoic acid and cinnamic acid
 - Found in the following products: fragrances, flavorings/spices (cola), pharmaceuticals (antifungal and antibacterial products), diaper powders and ointments, cough medicines, aperitifs
 - Cross-reacts with colophony, turpentine, benzoin, wood tar
2. Bergamot
 - Berloque dermatitis (see “Plant-Related Allergens”)
 3. Cinnamic aldehyde
 - Fragrance and flavor agent; constituent of cinnamon oil
 - When found in toothpaste, mouthwash, gum, patients may experience perioral dermatitis, tongue swelling, mouth ulceration
 - Flavoring in beverages (cola)
 - Spices: causes hand dermatitis in bakers
 - Essential oils: balsam of Peru, hyacinth, myrrh, patchouli, ceylon, cassia oil
 4. Lily of the valley
 - Allergen: hydroxycitronellal (synthetic)
 - Found in perfumes, soaps, cosmetics, eye cream, aftershaves
 - Also used in insecticides and antiseptics
 5. Musk ambrette
 - Fixative in perfumes
 - Photoallergen
 6. Oak moss absolute
 - *Evernia prunastri*: lichen oak moss
 - Main allergen: atranorin
 - Essential oil from lichens can contain the following other allergens: evernic acid and fumarprotocetic acid
 - “Masculine” odor in aftershaves
 7. Geraniol
 - *Sweet floral* odor of rose
 - Constitutes a large portion of rose and palmarose oil, geranium oil, lavender oil, jasmine oil, and citronella oil
 - Most widely used fragrance in perfumes, colognes, facial makeup, and skin-care products
 8. Eugenol
 - Powerful spicy odor of clove with a pungent taste
 - Found in oils of clove and cinnamon leaf
 - Also found in roses, carnations, hyacinths, and violets
 - Fragrance in perfume, cosmetics; flavoring in toothpaste, mouthwash; and food flavorings, dental cement, insecticidal and fungicidal properties—used to preserve meats and other foods
 9. Fragrance Mix I
 - Used as a screening tool for detecting fragrance allergy

FRAGRANCE-RELATED ALLERGENS

1. Balsam of Peru (also referred to as *Myroxylon pereirae*)
 - Wood extract derived from *Myroxylon balsamum* tree
 - Contains
 - Cinnamein (cinnamic acid, cinnamyl cinnamate, benzyl benzoate, benzoic acid and vanillin)

2. Bergamot
 - Berloque dermatitis (see “Plant-Related Allergens”)
3. Cinnamic aldehyde
 - Fragrance and flavor agent; constituent of cinnamon oil
 - When found in toothpaste, mouthwash, gum, patients may experience perioral dermatitis, tongue swelling, mouth ulceration
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TABLE 6-1 Topical Photoallergens

Group	INCI Name/Chemical Name/Trade Name*
Sunscreens	<p><i>UVB absorbers:</i></p> <p><i>para-Aminobenzoic acids (PABA):</i></p> <p>Amyl dimethyl PABA (<i>Padimate A</i>; <i>Escalol 506</i>)[†]</p> <p>PABA (<i>Pabanol</i>)[†]</p> <p>Ethylhexyl dimethyl PABA (octyl dimethyl PABA; <i>Padimate O</i>; <i>Escalol 507</i>)[†]</p> <p><i>Cinnamates:</i></p> <p>Cinoxate (2-ethoxyethyl-<i>p</i>-methoxycinnamate; <i>Phiasol</i>)</p> <p>Ethylhexyl methoxycinnamate (octyl methoxycinnamate; <i>Parsol MCX</i>; <i>Escalol 557</i>)</p> <p><i>Salicylate:</i></p> <p>Homosalate (metahomomenthyl salicylate; <i>Eusolex HMS</i>)</p> <p><i>UVA absorbers:</i></p> <p><i>Anthranillate:</i></p> <p>Menthyl anthranilate (cyclohexanol; <i>Trivent MA</i>)</p> <p><i>Benzophenones (partial UVB absorption):</i></p> <p>Benzophenone-3 (oxybenzone; <i>Escalol 567</i>)[†]</p> <p>Benzophenone-4 (sulisobenzene; <i>Escalol 577</i>)[†]</p> <p><i>Dibenzoylmethane:</i></p> <p>Butyl methoxydibenzoylmethane (avobenzene; <i>Parsol 1789</i>)[†]</p>
Fragrances	<p>6-Methylcoumarin[†]</p> <p>Musk ambrette[†]</p> <p>Sandalwood oil</p>
Antibacterials	<p>Dibromosalicylanilide (dibromsalan; DBS)[†]</p> <p>Tetrochlorosalicylanilide (TCSA; <i>Impregon</i>; <i>Irgasan BS200</i>)[†]</p> <p>Tribromosalicylanilide (tribromsalan; TBS)*</p> <p>Chlorhexidene (<i>Hibiclens</i>)</p> <p>Dimethylol-dimethyl hydantoin</p> <p>Hexachlorophene (<i>pHisoHex</i>)</p> <p>Bithionol (thiobisdichlorophenol; bisphenol; <i>Actamar</i>)[†]</p> <p>Dichlorophene (G4)</p> <p>Triclosan (<i>Irgasan DP300</i>)</p>
Antifungals	<p>Fentichlor (thiobischlorophenol)*</p> <p>Jadit (butylchlorosalicylamide; buclosamide)</p> <p>Multifungin (bromochlorosalicylanilide; BCSA)</p>
Others	<p>Chlorpromazine (<i>Thorazine</i>)*</p> <p>Clioquinol</p> <p>Ketoprofen (<i>Orudis</i>)</p> <p>Olaquinox</p> <p>Promethazine (<i>Phenergan</i>)*</p> <p>Quinidine (<i>Cardioquin</i>; <i>Quinidex</i>)</p> <p>Thiourea (thiocarbamide)</p>

*INCI: International Nomenclature of Cosmetic Ingredients.

†Commonly reported photoallergens.

Source: Freedberg IM et al. *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003, p. 1305.

TABLE 6-2 Systemic Photoallergens

Property	Generic Name (U.S. Trade Name)
Antifungal	Griseofulvin (<i>Fulvicin-U/F</i>)
Antimalarial	Quinine
Antimicrobials	Quinolone: Enoxacin (<i>Penetrex</i>), sulfonamides
Cardiac medication	Quinidine (<i>Quinaglute, Quinidex</i>)
Nonsteroidal	Ketoprofen (<i>Orudis, Oruvall</i>)
	Piroxicam (<i>Feldene</i>)
Vitamin	Pyridoxine hydrochloride (vitamin B6)

Source: Freedberg IM et al. *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003, p. 1305.

TABLE 6-3 Topical Phototoxic Agents

Agent	Exposure
Rose bengal	Ophthalmologic examination
Antimicrobials	Occur naturally in plants, fruits and vegetables (lime, lemon, celery, fig, parsley, and parsnip); used in perfumes and cosmetics; used for topical photochemotherapy
Tar	Topical therapeutic agent; roofing materials

Source: Freedberg IM et al. *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003, p. 1301.

- Constituents: α -amylcinnamic alcohol, cinnamic alcohol, cinnamic aldehyde, eugenol, geraniol, hydroxycitronellal, isoeugenol, oak moss absolute
 - Along with balsam of Peru, Fragrance Mix I detects the majority of patients with a fragrance allergy

10. Fragrance Mix II

 - New fragrance mixture for patch testing
 - Constituents: hydroxyisohexyl 3-cyclohexene carboxyaldehyde (Lyrall), Citral, farnesol, citronellol, hexyl cinnamal, coumarin
 - Lyrall is the most common sensitizer in the mix
- HAIR-RELATED ALLERGENS**

1. Paraphenylenediamine (PPD)

 - Blue-black aniline dye
 - Dark permanent hair dye: hand dermatitis in hairdressers, scalp/hairline dermatitis in clients

2. Glycerol thioglycolate (GTG)

 - Dyed furs, photographic developers, photocopy, printing ink, dark cosmetics, black rubber (rubber antioxidant), leather processing
 - Cross-reacts with PABA, ester anesthetics, sulfa medications, azo dyes (textile dermatitis)
 - Synthetic henna: formulations are available that contain PPD and sometimes lead to an allergic reaction (Type IV hypersensitivity)
 - Natural henna is derived from the *Lawsonia alba* plant and does not usually lead to ACD
 - Patch test with PPD

2. Glycerol thioglycolate (GTG)

 - Acidic (salon) permanent wave solutions and hair straighteners
 - Chemical remains in hair shaft for months: chronic dermatitis in hairdressers and clients
 - Note: Alkaline (home) permanent solutions contain ammonium thioglycolate (ATG) and are also irritating

TABLE 6-4 Systemic Phototoxic Agents

Property	Generic Name (U.S. Trade Name)	Property	Generic Name (U.S. Trade Name)
Antianxiety drugs	Alprazolam (<i>Xanax</i>) Chlordiazepoxide (<i>Librax</i> ; <i>Librium</i> ; <i>Limbitrol</i>)	Antipsychotic drugs (<i>cont.</i>)	Prochlorperazine (<i>Compazine</i>)* Thioridazine (<i>Mellaril</i>) Trifluoperazine (<i>Stelazine</i>)
Anticancer drugs	Dacarbazine (<i>DTIC-Dome</i>) Fluorouracil (<i>Adrucil</i>) Methotrexate (<i>Rheumatrex</i>) Vinblastine (<i>Velban</i>)	Cardiac medications	Amiodarone (<i>Cordarone</i> ; <i>Pacerone</i>)* Quinidine (<i>Quinaglute</i> ; <i>Quinidex</i>)
Antidepressants	Tricyclics: Amitriptyline (<i>Elavil</i> ; <i>Limbitrol</i> ; <i>Triavil</i>) Desipramine (<i>Norpramin</i>) Imipramine (<i>Tofranil</i>)	Diuretics	Furosemide (<i>Lasix</i>)* Thiazides: Bendroflumethiazide (<i>Corzide</i>) Chlorothiazide (<i>Aldoclor</i> ; <i>Diuril</i>)* Hydrochlorothiazide (<i>Accuretic</i> ; <i>Aldactazide</i> ; <i>Aldoril</i> ; <i>Atacana Avalide</i> ; <i>Capozide</i> ; <i>Dlovan</i> ; <i>Dyazide</i> ; <i>HydroDIURIL</i>)*
Antifungal	Griseofulvin (<i>Fulvicin</i> ; <i>Grifulvin V</i> ; <i>Gris-PEG</i>)	Dye	Fluorescein (<i>AK-Fluor</i> ; <i>Fluor</i> ; <i>Fluor-I-Strip Fluorescite</i>) Methylene blue (<i>Urised</i>)
Antimalarials	Chloroquine (<i>Aralen</i>) Quinine	Furocoumarins	Psoralens: 5-Methoxypsoralen* 8-Methoxypsoralen (<i>Oxsoralen-Ultra</i> 4,5',8-Trimethylpsoralen*)
Antimicrobials	Quinolones: Ciprofloxacin (<i>Cipro</i>) Enoxacin (<i>Penetrex</i>) Gemifloxacin Lomefloxacin (<i>Maxaquin</i>)* Moxifloxacin (<i>Avelox</i>) Nalidixic acid (<i>NegGram</i>)* Norfloxacin (<i>Chibroxin</i> ; <i>Noroxin</i>) Ofloxacin (<i>Floxin</i> ; <i>Ocuflox</i>) Sparfloxacin (<i>Zagam</i>)* Suifonamides Tetracyclines Demeclocycline (<i>Declomycin</i>)* Doxycycline (<i>Monodox</i> ; <i>Periostat</i> ; <i>Vibramycin</i>)* Minocycline (<i>Dynacin</i> ; <i>Minocin</i>) Tetracycline (<i>Helidac</i> ; <i>Sumycin</i>) Trimethoprim (<i>Bactrim</i> ; <i>Polytrim</i> ; <i>Primsal</i> ; <i>Sepra</i>)	Hypoglycemics	Sulfonylureas: Acetohexamide Chlorpropamide (<i>Diabinese</i>) Glipizide (<i>Glucotrol</i>) Glyburide (<i>DiaBeta</i> ; <i>Glucovance</i>) <i>Glynase Pres Tab</i> ; <i>Micronase</i>) Tolazamide (<i>Tolinase</i>) Tolbutamide (<i>Orinase</i>)*
Antipsychotic drugs	Phenothiazines: Chlorpromazine (<i>Thorazine</i>)* Perphenazine (<i>Triavil</i> ; <i>Trilafon</i>)	NSAIDs	Acetic acid derivative: Diclofenac (<i>Arthrotec</i> ; <i>Cataplan Voltaren</i>) Anthranilic acid derivative: Mefenamic acid (<i>Ponstel</i>) Enolic acid derivative: Piroxicam (<i>Feldene</i>)*

(Continued)

TABLE 6-4 (Continued)

Property	Generic Name (U.S. Trade Name)	Property	Generic Name (U.S. Trade Name)
NSAIDs (<i>cont.</i>)	Propionic acid derivatives: Ibuprofen (<i>Advil; Motrin; Nuprin Vicoprofen</i>) Ketoprofen (<i>Orudis; Oruvail</i>) Naproxen (<i>Aleve; Naprelan; Naprosyn</i>)* Oxaprozin (<i>Daypro</i>) Tiaprofenic acid	Photodynamic therapy agents	Porfimer (<i>Photofrin</i>)* Verteporfin (<i>Visudyne</i>)*
	Salicyclic acid derivative: Diflunisal (<i>Dolobid</i>) Others: Celecoxib (<i>Celebrex</i>) Nabumetone (<i>Relafen</i>)*	Retinoids	Acitretin (<i>Soriatane</i>) Isotretinoin (<i>Accutane</i>) Etretinate
		Other	Flutamide (<i>Eulexin</i>) Hypericin Pyridoxine (vitamin B6) Ranitidine (<i>Zantac</i>)
*Commonly reported. Source: Freedberg IM et al. <i>Fitzpatrick's Dermatology in General Medicine</i> , 6th Ed. New York: McGraw-Hill; 2003, p. 1302.			

3. Ammonia persulfate
 - Peroxide hair bleaches
 - Bleached baking flour
 - Contact urticaria and anaphylactoid reactions

4. Cocamidopropyl betaine
 - Allergen may be dimethylaminopropylamine or amidoamine (residues from synthesis)
 - Surfactant
 - Shampoo (dermatitis in hair dressers), liquid soaps
5. Wool alcohols
 - Lanolin and lanolin alcohol
 - From the sebum of sheep
 - Lanolin consists of 95% wool esters: alcohols (52%) and acids (48%)

MEDICINE-RELATED ALLERGENS

1. Tixocortol pivalate
 - Used to test for allergy to group A steroids (e.g., prednisone, hydrocortisone)
 - Short-chain esters
2. Budesonide
 - Screening agent for allergy to groups B (e.g., triamcinolone) and D2 (e.g., HC-17 butyrate) steroids
 - Cross reactions may be seen between Groups A and D2, and between Groups B and D2
 - Long-chain steroids
3. Ethylenediamine dichloride
 - Stabilizer in topical creams, medicines, dyes, rubber, resin, waxes, insecticides, asphalt, fungicides
 - Previously found in nystatin cream
 - Cross-reacts with aminophylline, antihistamines (hydroxyzine), meclizine (antivert)
4. Glutaraldehyde (Fig. 6-1)
 - Cold sterilizing solution (medical/dental equipment)



FIGURE 6-1 Chronic fingertip dermatitis due to glutaraldehyde allergy in an assistant sterilizing colonoscopy equipment. (Courtesy of Dr. Giuseppe Militello.)

- Wool alcohols are used to test for lanolin allergy
- Topical creams (e.g., Eucerin), cosmetics, adhesives, topical steroids
- 6. Propylene glycol
 - A dimer alcohol used to make drugs more soluble
 - Vehicle base in pharmaceuticals (Valium, ECG and lubricant jelly), cosmetics, food, and topical medications (corticosteroid creams, ointments, foams, gels, and solutions)
 - Brake fluid, tobacco formulations, antifreeze
- 7. Thimerosol
 - Mercury-containing organic compound (an organomercurial)
 - Made from the combination of ethyl mercuric chloride, thiosalicylic acid, sodium hydroxide, and ethanol
 - Preservative in vaccines: influenza (flu) vaccines and tetanus and diphtheria vaccines (Td and DT) are not available without thimerosol
 - Also found in antitoxins, immunoglobulins
 - False-positive intradermal testing (e.g., to tuberculosis) can occur if material is preserved with thimerosol
 - Eye/ear drops, nasal sprays, contact lens solutions: conjunctivitis, eyelid dermatitis
 - Cosmetics, liquid soap, oral hygiene products, pesticides
 - Cross-reacts with piroxicam, mercury
 - Most reactions seen with patch testing are not relevant and are indicative of prior exposure (e.g., vaccines)
- 8. Neomycin sulfate
 - Antibiotic in the aminoglycoside group
 - Used topically in ointments, creams, ear drops, and eye drops
 - Cross-reacts with gentamycin, tobramycin, streptomycin, or any systemic aminoglycoside
 - Often cosensitivity to bacitracin
- 9. Triclosan
 - Antibacterial agent
 - Soap, shampoo, mouthwash
- 10. Benzocaine
 - Topical anesthetic (remedies for hemorrhoids, sunburn, toothaches, sore throats, athlete's foot)
 - Cross-reacts with ester anesthetics, PABA, paraphenylenediamine, sulfa medications
 - Patch test with caine mix: benzocaine, dibucaine hydrochloride, and tetracaine hydrochloride

NAIL-RELATED ALLERGENS

- Contact dermatitis to nail allergens may present as chronic paronychia, onychodystrophy, fingertip dermatitis, or face and neck dermatitis (ectopic dermatitis)

1. Ethyl cyanoacrylate
 - Instant glue ("Super Glue"), artificial nail glue
 - Liquid bandages, sealant for ileostomy appliances
 - Electronic circuit boards, aircrafts, automobiles
2. Methyl methacrylate
 - Clear, rigid plastic (artificial nails, hard contact lenses, hearing aids, dentures, dental fillings/sealants)
 - Glue for surgical prostheses/artificial joints: dermatitis in orthopedic surgeons
 - Cross-reacts with ethyl methacrylate
3. Toluene-sulfonamide (tosylamide) formaldehyde resin
 - Used in nail polishes
 - Nail polish: eyelid, face, neck, finger dermatitis

PLANT-RELATED ALLERGENS

1. *Pinaceae*
 - Pine trees (i.e., *Pinus* species) and spruce trees
 - Source of colophony (or wood rosin)
 - Main allergens of colophony are oxidation products of abietic acid and its isomer primaric acid
 - Found in medical adhesives, cosmetics, athletic grip aids, dental cement, violin bow rosin, newsprint/magazine paper, soldering materials, nail coating (construction workers)
 - Cross-reacts with balsam of Peru
 - Source of turpentine, oleoresin also contains irritants, such as alpha-pinene, and allergens, such as delta-3-carene
2. *Alliaceae*
 - Genus *Allium*
 - Includes onions, garlic, and chives
 - Allergens: diallyldisulfide, allylpropyl disulfide, and allicin
 - Fresh garlic is both an allergen and a potent irritant
 - Causes second- and third-degree burns when applied to injured skin
 - Most common cause of fingertip dermatitis in housewives and caterers
3. Lichens
 - Allergens: usnic acid, atranorin, evernic acid, fumarprotocetraric acid
 - Forest workers, gardeners, woodcutters
 - Lichen extracts (oak moss, tree moss): dermatitis from aftershave products
4. *Primulaceae* (Fig. 6-2)
 - *Primula obconica*: primrose
 - Allergen is primin
 - Highly allergenic petals and sepals
 - May cross-react with other quinones: orchids or tropical woods, such as teak, rosewood



FIGURE 6-2 Primulaceae. (Courtesy of Dr. Kiyoshi Isono.)



FIGURE 6-3 Family asteraceae.

5. Family *Asteraceae* (previously *Compositae* family) (Fig. 6-3)

- Ragweed, chrysanthemum, feverfew and carrot weed, daisy, sunflower, dandelion, artichoke, lettuce, and endives
 - Gardeners, florists, farmers, cooks: airborne or summer-exacerbated dermatitis
 - Allergen: *Sesquiterpene lactone (SQL)*
 - Found in the leaves, stems, flowers, and some pollen
 - Cross-reactivity occurs randomly
 - SQL mix (i.e., alantolactone, dehydrocostus lactone, costunolide) is not very sensitive
 - Compositae mix (arnica, yarrow, tansy, German chamomile and feverfew) may be a more sensitive mix
 - Ragweeds (*Ambrosia* species)
 - Oleoresin is thought to cause airborne contact dermatitis
 - Typically occurs in atopic patients
 - Feverfew and carrot weed (*Parthenium hysterophores*)
 - Chrysanthemum (*Dendranthema grandiflorum* cv.): most common *Asteraceae* plants that cause occupational contact dermatitis
 - Sunflower (*Helianthus annuus*)
 - 1-0-methyl 1-4,5-dihydroniveusin A
 - Trichomes, or small hairs, on the surfaces of the leaf secrete the allergen
 - Windblown trichomes from dry plants can cause airborne contact dermatitis
 - Dandelion (*Taraxacum officinale*)
 - Airborne allergic contact dermatitis
 - Allergen is taraxinic acid (1-0-*b*-glucopyranoside)
6. Toxicodendron
- Species (*Rhus*); family (*Anacardiaceae*)
 - Allergens are pentadecylcatechols, found in the plant sap
 - Urushiol (milky secretion)
 - Oleoresin (dry resin)
 - Cathecols are soluble in rubber
 - Particles suspended in smoke can carry urushiol
 - Blister fluid does not contain urushiol
 - Nonleaf portions of the plant can induce dermatitis
 - Most common cause of contact dermatitis in children
 - Poison ivy
 - *T. radicans*: climbing vine, eastern United States
 - *T. rydbergii*: nonclimbing dwarf shrub, the northwestern United States (Fig. 6-4)
 - Poison oak
 - *T. diversilobum*, western United States
 - *T. toxicarium*, eastern United States (Fig. 6-5)
 - Poison sumac: *T. vernix*
 - Identification
 - *Poison ivy and poison oak*: 3 to 5 leaflets per compound leaf
 - *Poison sumac*, 7 to 13 leaflets per leaf; have smooth edges
 - Cross-reacting substances
 - Cashew nut tree: entire tree except for the cashew nut
 - Indian marking tree: black juice (used as a laundry marker, causes Dhobi itch)
 - Japanese laquer tree: viscous sap that is used for varnishing wood; polymerized urushiol persists in the lacquer
 - Brazilian pepper tree: sap and crushed berries



FIGURE 6-4 Poison ivy.

- Mango tree: skin of the fruit and the leaves, bark, and stems of the plant contain sensitizing resorcinols; pulp of the fruit is nonallergenic
- Ginkgo tree: anacardic acid, which is present in the seed pulp

7. *Liliaceae*

- Tulips, hyacinths, and asparagus
- Tulip fingers
- Combined allergic and irritant contact dermatitis
- Allergen: tuliposide A is converted to tulipalin A, the allergen, by means of acidic hydrolysis

8. *Alstroemeriaceae* family (Peruvian lily)

- Tuliposide A and B are found in virtually all portions of the plant
- Flowers contain more allergen than the stems; the leaves have the smallest amount of allergen
- Most common cause of allergic hand dermatitis in florists

9. Phytophotodermatitis

- Phytophotodermatitis results in hyperpigmentation (Fig. 6-6)
- *Berloque dermatitis* is due to bergamot oil; UV light reacts with bergapten (a furocoumarin) and induces melanogenesis
- Most common plant families *Umbeliferae* (most common), *Rutaceae*, and *Moraceae*
 - *Umbeliferae*: cow parsley, parsley, celery, carrot, fennel, cow parsnip, hogweed, parsnip
 - *Rutaceae*: lime, lemon, grapefruit, mokihana (Hawaiian leis), rue
 - *Moraceae*: fig



FIGURE 6-5 Poison oak.



FIGURE 6-6 Phytophotodermatitis. (Courtesy of Dr. Asra Ali.)

- Allergens can be found in perfumes and fragrances, cosmetics, toiletries, soap, household cleaners, detergents, air fresheners
- 10. Contact urticaria from plants
 - Roasted chili peppers contain capsaicin
 - *Urticaceae* family: stinging nettle (*Urtica dioica*)
 - Irritant chemicals, which include acetylcholine, histamine, and 5-hydroxytryptamine
- 11. Chemical irritant dermatitis
 - Most common dermatitis in florists
 - *Dieffenbachia picta* (*Araceae*), also known as dumb cane: calcium oxalate
 - Daffodil itch: calcium oxalate in the sap

Rubber Allergens

1. Latex
 - Milky fluid derived from rubber tree *Hevea brasiliensis*
 - Composed primarily of *cis*-1,4-polyisoprene
 - Reaction can involve irritant dermatitis, immediate (type I) hypersensitivity; rarely may cause delayed (type IV) hypersensitivity
 - Multiple episodes of contact urticaria with scratching can lead to clinical appearance of chronic dermatitis
 - Gloves, condoms, balloons, rubber adhesives
 - Corn starch powder—with which gloves are dusted—is a potent carrier of latex proteins
 - Health care workers, rubber industry workers, children with spina bifida or urogenital abnormalities
 - In vitro tests: radioimmunoassay tests (RAST) for IgE
 - Cross-reaction
 - Food: bananas, avocados, chestnuts, kiwis
 - Shared IgE epitopes: ragweed, grasses, and *Ficus* trees
2. Rubber accelerators and other rubber related allergens
 - Rubber accelerators are chemicals used to speed up the manufacturing process of rubber (vulcanization); sulfur cross-links the polymer chains in the latex
 - Carbamates (carba mix)
 - Rubber accelerator
 - Rubber dermatitis in bleached fabrics (waistbands, bra straps)
 - Consumer rubber products (condoms, swimwear, makeup sponges, eyelash curlers, gloves, shoes)
 - Cross-reacts with thiurams
 - Mercaptobenzothiazole (MBT, mercapto mix)
 - Rubber accelerator
 - Most common cause of allergic shoe dermatitis (Fig. 6-7)



FIGURE 6-7 Typical distribution of an allergic shoe dermatitis. (Courtesy of Dr. Giuseppe Militello.)

- Rubber products: gloves, makeup sponges, rubber in undergarments/clothing, swimwear
- Also in tires, condoms, antifreeze, fungicides, flea and tick powders, photographic film emulsions, adhesives, bactericides, and is an anticorrosive agent in cutting oils and greases
- Thiuram mix
 - Most common rubber additives to cause a type IV reaction
 - Found in almost all rubber products, shoes, gloves, condoms, elastic bands, and ingredients of pesticides, insect repellents, antiscabies medication, fungicides, wood preservatives, paint additives, lubricating oils, and the drug disulfiram (Antabuse)
- Thiourea
 - commonly tested with a dialkyl thiourea mix
 - common source is neoprene rubber

Antioxidants

- Added to decrease the rate of rubber degradation
- Substituted phenols are used for latex gloves

PRESERVATIVES

1. Formaldehyde
 - Released from the proallergen N-hydroxymethyl succinimide
 - Cleaved into succinimide and formaldehyde when it comes in contact with the transepidermal water on the surface of the skin

2. Formaldehyde is the active allergenic compound
 - Textile resins
 - Permanent press or wrinkle-resistant textiles (urea-formaldehyde, melamine formaldehyde)
 - Cosmetics, household products, ink, latex paint, pathology fixatives, fertilizer, embalming solution, insulation
 - Formaldehyde resins
 - *p*-tert-butylphenol formaldehyde resin (common shoe allergen)
 - ▲ Leather adhesive
 - ▲ Other uses: waterproof glues and finishes
 - Formaldehyde-releasing preservatives
 - Quaternium-15 (most common): cosmetics, lotions, creams, shampoos and soaps, polishes, cleaners, cutting fluids, and paints
 - Imidazolidinyl urea (Germall 115, Euxyl K200)
 - Diazolidinyl urea (Germall II)
 - DMDM hydantoin
 - 2-Bromo-2-nitropane-1,3-diol (Bronopol)
3. Non-formaldehyde-releasing preservatives
 - Methylidibromo glutaronitrile (MDBGN)
 - Parabens
 - Most used topical preservatives worldwide
 - Paraben Paradox: some sensitized patients only react to parabens when applied to dermatitic skin (e.g., leg ulcer patients)
 - Medical creams, lotions, pastes, and several cosmetics and skin care products; food preservatives; industrially in oils, fats, and glues
 - Isothiazolinones
 - Kathon CG: combination of methylchloroisothiazolinone and methylisothiazolinone
 - Cosmetics and commercial household products such as shampoos, creams, lotions, cleaners, and washing materials; it is also a widely used industrial preservative for cutting fluids

METAL ALLERGENS

1. Nickel
 - Most common cause of patch test reactions
 - Jewelry, clothing (snaps, zippers, and buttons), coins, keys, other metals; gold less than 18 carats can contain nickel
 - Also used for nickel plating, to color ceramics, to make some batteries
 - Foods naturally high in nickel include chocolate, soybeans, nuts, and oatmeal
 - Dimethylglyoxime test is used to detect nickel
 - Rub on the item; if solution turns color (pink to reddish), it indicates a positive reaction
 - Indicates the presence of nickel in a concentration of at least 1:10,000

2. Potassium dichromate
 - Chromates (chrome)
 - Usually found as chrome salts
 - Cement, leather tannin, ceramics, paint, match heads, suture, bleach/detergents, numerous industrial chemicals, green felt of card tables, glues
 - Green tattoo and cosmetic pigments
 - Green textile dyes (military green, green pool table felt)
3. Gold
 - A gold salt, gold sodium thiosulfate, is used for patch testing
 - A common allergen in eyelid dermatitis
 - Positive reactions may not be clinically relevant (positive patients usually tolerate their gold jewelry)

COLORS AND DYE ALLERGENS

Tattoos

- Ink particles are found within large phagosomes in the cytoplasm of both keratinocytes and phagocytic cells
- Allergic reactions to red tattoo pigments are the most common (Table 6-5)
- Photoaggravated reactions: most commonly yellow dye
- Foreign-body reaction: most commonly red (mercury)
- Tattoo-induced pseudolymphoma: most commonly red

Dyes

- Disperse Blue 106 and 124 are the most common dye allergens in textile dermatitis

ADHESIVES

Epoxy Resin

- Two-component adhesives
- Most common allergens: bisphenol A and epichlorohydrin
- Glue, laminates, eyeglass frames, vinyl gloves, handbags, plastic necklaces, dental bonding agents, microscopy immersion oil, floor coverings

OTHER ALLERGENS

Sodium Hypochlorite

- Chlorinated swimming pools
- Bleach

TABLE 6-5 Tattoo Components

Tattoo Color	Component
Blue	Cobalt aluminate
Brown	Ferric oxide
Green	Chromic oxide, lead chromate, phthalocyanine dyes
Red	Cinnabar (mercuric sulfide), sienna (ferric hydrate), sandalwood, brazilwood, organic pigments (aromatic azo compounds)
Yellow	Cadmium sulfide
Black	Carbon (India ink), iron oxide, logwood
Purple	Manganese, aluminum
White	Titanium oxide, zinc oxide

PATCH TESTING

- T.R.U.E. Test (allergen patch test) (Table 6-6)
 - Ready-to-use contact allergen test
 - Contains 28 allergens and allergen mixes
 - Test also contains one negative control: uncoated polyester patch
 - Allergen mixes incorporated into hydrophilic gels attached to a waterproof backing
- Perspiration and transepidermal water loss rehydrate the dried gel layer, thereby releasing the allergens onto the skin
- T.R.U.E. Test is removed after 48 hours
- Reactions are interpreted at 72 to 96 hours after test application
- Fragrance mix
 - Contains eight allergens
 - Geraniol, cinnamaldehyde, hydroxycitronellal,

TABLE 6-6 True Test Panels

Panel 1.1	Panel 2.1	Panel 3.1
1. Nickel sulfate	13. <i>p</i> - <i>tert</i> -Butylphenol formaldehyde resin	25. Diazolidinyl urea
2. Wool alcohols	14. Epoxy resin	26. Imidazolidinyl urea
3. Neomycin sulfate	15. Carba mix	27. Budesonide
4. Potassium dichromate	16. Black rubber mix	28. Tixocortol pivalate
5. Caine mix	17. Cl + Me-isothiazolinone	29. Quinoline mix
6. Fragrance mix	18. Quaternium-15	
7. Colophony	19. Mercaptobenzothiazole	
8. Paraben mix	20. <i>p</i> -Phenylenediamine	
9. Negative control	21. Formaldehyde	
10. Balsam of Peru	22. Mercapto mix	
11. Ethylenediamine dihydrochloride	23. Thimerosal	
12. Cobalt dichloride	24. Thiuram mix	

- cinnamyl alcohol, eugenol, isoeugenol, *α*-amylcinnamaldehyde, and oak moss
- Mercapto mix
 - Composed of three chemical accelerators: benzothiazole sulfenamide derivatives
 - *N*-Cyclohexylbenzothiazyl-sulfenamide, dibenzothiazyl disulfide, and morpholinylmercaptobenzothiazole
- Thiuram mix
 - Composed of four substances in equal parts
 - Tetramethylthiuram monosulfide, tetramethylthiuram disulfide, disulfiram, dipentamethylenethiuram disulfide
 - Black rubber mix: *N*-Isopropyl-*N'*-phenylparaphenylenediamine, *N*-cyclohexyl-*N'*-phenyl paraphenylene-diamine, *N*, *N'*-diphenyl paraphenylenediamine
- Carba mix
 - Chemicals used to stabilize rubber products
 - Diphenylguanidine, zincdibutylidithiocarbamate, and zincdiethyldithiocarbamate in equal parts
- Repeat open application test (ROAT)
 - For individuals who develop weak or 1 + positive reactions to a chemical in the T.R.U.E Test
 - Useful in determining whether the reaction is significant or in personal product testing (only leave-on products should be tested)
 - Consists of rubbing in the product twice daily for several days to the skin of the antecubital fossa
 - A reaction often consists of erythematous papules
 - Samples of the individual ingredients used by the cosmetic manufacturer may be requested and tested on the individual
- Finn chamber system
 - Allows for customized patch testing and flexibility
 - Employs a multiwell aluminum patch (Fig. 6-8)
 - Most common size is 8-mm chamber applied to Scanpor tape in two rows of five
 - Each well is filled with a small amount of the allergen being tested, and the patch is taped to normal skin on the patient's upper back
 - After 48 hours, the patch is removed, and an initial reading is taken
 - Second reading is made a few days later; each 8-mm chamber holds 20 μ L



FIGURE 6-8 Finn chamber system for patch testing. (Courtesy of Dr. Giuseppe Militello.)

- A. Diazolidinyl urea
 - B. DMDM hydantoin
 - C. Imidazolidinyl urea
 - D. Quaternium 15
 - E. Melamine formaldehyde
2. Ethylcyanoacrylate is used in which of the following cosmetic nail products?
 - A. Acrylic nails
 - B. Nail enamel
 - C. Pre-formed plastic tips
 - D. Silk wraps
 - E. C and D
3. Which of the following is the most common photoallergen?
 - A. Padimate A
 - B. Padimate O
 - C. Benzophenone 3 (oxybenzone)
 - D. PABA
 - E. Menthyl anthranilate
4. Which of the following is a screening agent for triamcinolone allergy?
 - A. Tixocortol pivalate
 - B. Budesonide
 - C. Clobetasol
 - D. Hydrocortisone butyrate
 - E. Desoximethasone

QUIZ

Questions

1. Which of the following formaldehyde related allergens is associated with textile dermatitis?

5. Diallyldisulfide is the allergen found in which plant?
 - A. Garlic
 - B. Lichen
 - C. Ragweed
 - D. Feverfew
 - E. Daisy
 6. Which of the following is used to screen for epoxy allergy?
 - A. Ethyl acrylate
 - B. Glyceryl thioglycolate
 - C. Dimethylaminopropylamine
 - D. Diglycidyl ether of bisphenol A
 - E. Polyurethane
 7. Patients sensitized to urushiol can react to which of the following plants?
 - A. Cashew
 - B. Indian marking nut
 - C. Japanese lacquer tree
 - D. Mango
 - E. All of the above
 8. Which of the following metals is most commonly implicated in tattoo reactions?
 - A. Chromic oxide
 - B. Cobalt aluminate
 - C. Cinnabar (mercuric sulfide)
 - D. Ferric oxide
 - E. Cadmium sulfide
 9. Which of the following professions is at a higher risk for allergic contact dermatitis to glutaraldehyde?
 - A. Florist
 - B. Chef
 - C. Car mechanic
 - D. Dental assistant
 - E. Hairdresser
 10. Which of the following statements about thimerosal is true?
 - A. The majority of reactions are relevant to a patient's dermatitis.
 - B. It is a preservative in certain vaccines.
 - C. It is an arsenical compound.
 - D. It is not on the T.R.U.E. Test.
 - E. None of the above
- topical medicaments. Diazolidinyl urea, imidazolidinyl urea, quaternium 15, and DMDM hydantoin are formaldehyde releasers used in such products. Melamine formaldehyde is one of several formaldehyde releasers used as a finishing resin in permanent press or "wrinkle-free" clothing. Patients may react to the resin or the formaldehyde itself. Other resins include urea formaldehyde and cyclized urea derivatives. Another group of allergens involved in textile dermatitis are the disperse dyes, of which the Disperse Blue dyes 106 and 124 are the most common allergens.
2. E. Ethylcyanoacrylate is used to adhere plastic nail tips and silk wraps to the nail plate. It is a rare allergen in nail cosmetics and does not cross react with other acrylic compounds which are used in nail products. Ethyl acrylate and methylmethacrylate are used to screen for acrylic nail allergy. The major allergen in nail enamel is toluene sulfonamide formaldehyde resin, also known as tosylamide formaldehyde resin.
 3. C. Benzophenone 3 (oxybenzone) is a widely used sunscreen agent, and as a result has become the most common sunscreen chemical to cause allergy and photo-allergy. PABA and its derivatives used to be the most common allergens but after they were reported to be allergens, they were largely removed from products and subsequent sunscreens were marketed as "PABA free." Padimate A and O are PABA derivatives. Menthyl anthranilate is a UVA absorber and a rare allergen.
 4. B. Corticosteroids are organized into five groups according to chemical structure. Group A consists of hydrocortisone, hydrocortisone acetate, prednisone, and methylprednisolone. Tixocortol pivalate is the screening agent for group A allergy. Group B involves triamcinolone, fluocinolone acetonide, desonide, and budesonide. Screening agent for this group is budesonide. Group C steroids include desoximethasone and clocortolone pivalate; this is the least allergenic class. Group D is subcategorized into D1 and D2 classes. Clobetasol is in group D1, while hydrocortisone butyrate and valerate are found in group D2. Group D2 may cross react with group A and budesonide.
 5. A. Diallyldisulfide is the allergen found in garlic and is a common cause of fingertip dermatitis in chefs and food handlers. Usnic acid is the allergen found in lichens and commonly affects forest workers and woodcutters. Ragweed, feverfew, and daisies belong to the *Asteracea* family of plants. The main allergens in this family are the sesquiterpene lactones.
 6. D. Epoxy resin systems are used to manufacture plastics and adhesives. The basic building block or monomer of epoxy resin is diglycidyl ether of

Answers

1. E. Formaldehyde and its releasers are common preservatives in cosmetic products and

bisphenol A which is formed by combining bisphenol A and epichlorhydrin. Monomers are then polymerized with the help of curing agents or hardeners into polymerized plastics. Epoxy plastics that are fully polymerized are not allergenic. Reactions are usually occupational or to products that are contaminated with uncured monomer. Ethyl acrylate is a screening agent for acrylic plastics or polymers. Contact dermatitis is frequently encountered in nail cosmetics, Dimethylaminopropylamine is a byproduct in the manufacture of cocamidopropylbetaine, a surfactant in shampoos. Glyceryl thioglycolate is used in the acidic permanent wave solutions and can remain allergenic in the hair shaft for months. Polyurethane is a plastic manufactured by the polymerization of isocyanates.

7. E. The allergen in poison ivy, sumac, and oak is urushiol. These plants belong to the *Anacardiaceae* family. Patients may react to chemical derivatives of urushiol found in other plants in the same family. Cashew, Indian marking nut, Japanese lacquer, and mango all belong to the *Anacardiaceae* family.
8. C. Most allergic reactions in tattoos are to the red pigment. Cinnabar or mercuric sulfide is a common metal in red tattoos. Chromic oxide, cobalt aluminate, ferric oxide, and cadmium sulfide are found in green, blue, brown, and yellow tattoos, respectively.
9. D. Glutaraldehyde is used in cold sterilizing solutions. Allergic reactions are commonly seen in workers involved in cleaning medical equipment such as dental assistants.
10. B. Thimerosal is an organic compound commonly found in vaccines. It was also used as a preservative in ophthalmic solutions but has been removed from most consumer products. The majority of

thimerosal patch test reactions are not relevant to a patient's dermatitis, but rather an indication of past sensitization, most likely from childhood vaccinations. Thimerosal is one of the allergens found on the T.R.U.E. Test (Allerderm).

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AUTOIMMUNE BULLOUS DISEASES

WHITNEY HIGH

TERMINOLOGY

Indirect Immunofluorescence

- Goal: to detect circulating autoantibodies in the serum that are purposefully reacted with a test substrate
- Use of serum containing an antibody of interest is directed against a substrate, such as monkey esophagus or rat bladder, which is then followed “indirectly” by the addition of fluorescein-conjugated human anti-immunoglobulin to label the resultant complex

Direct Immunofluorescence

- Goal: to detect antibody and immunoreactants already deposited in tissue of interest
- Use of fluorescein-conjugated antibodies directed against complement fractions and immunoglobulins (IgG, IgM, and IgA) that are placed “directly” on sections of tissue

Direct Immunofluorescence (DIF) on Salt-Split Skin

- Incubate the patient’s skin biopsy sample in 1 mol/liter saline to induce a split through the lamina lucida prior to performing the DIF testing
- Allows for differentiation of immunobullous diseases by indicating the location of deposition of immunoreactants in the split skin (i.e., above or below the lamina lucida)
 - Immunoreactants deposit in the “roof” (above the split) in bullous pemphigoid
 - Immunoreactants deposit in the “floor” (below the split) in
 - Bullous systemic lupus erythematosus (SLE)

- Antiepiligrin cicatricial pemphigoid (autoantibodies to laminin-5 and laminin-6)
- Anti-p105 pemphigoid (autoantibodies to a 105-kDa lower lamina lucida protein)
- Epidermolysis bullosa acquisita (EBA)

Nikolsky’s Sign

- Lateral pressure applied to edge of bulla
- Positive test if bulla extends laterally with pressure
- Suggests extreme pidermal fragility
- Common causes of a positive Nikolsky sign include:
 - Staphylococcal scalded skin syndrome (Ritter disease)
 - Toxic epidermal necrolysis
 - Pemphigus vulgaris

AUTOIMMUNE BULLOUS DISEASES

Bullous Pemphigoid (Fig. 7-1)

- Autoimmune, subepidermal, blistering skin disease
- The single most common immunobullous disease in dermatology
- Clinical
 - Usually an older patient (> 60 years), often with other co-morbidities
 - Does not normally begin in the mucosa (unlike pemphigus)
 - May begin as an urticarial eruption, often intensely pruritic
 - Tense blisters and bullae
 - Common locations include the abdomen, flexor forearms, and inner thighs



FIGURE 7-1 Bullous pemphigoid. (Courtesy of Dr. Robert Jordon.)

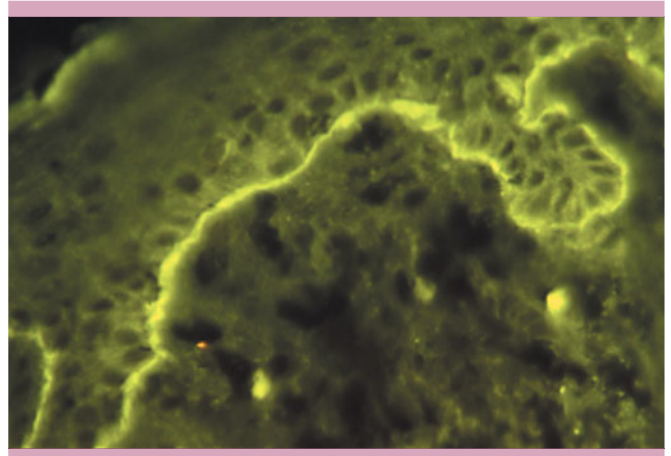


FIGURE 7-2 Bullous pemphigoid immuno fluorescence. (Courtesy of Dr. Robert Jordon.)

- Nikolsky's sign is negative
- Rarely involves mucous membranes: 10% to 35%
- Drugs associated with bullous pemphigoid include: furosemide, ibuprofen and other nonsteroidal anti-inflammatory agents, captopril, penicillamine, and antibiotics
- Diagnosis
 - Histology: subepidermal blistering process, usually with prominent eosinophils in the blister cavity and superficial dermis
 - Antigens
 - Bullous pemphigoid antigen 1 (BPAgI)
 - ▲ 230 kDa
 - ▲ Intracellular portion of hemidesmosome plaque, part of the plakin superfamily
 - Bullous pemphigoid antigen 2 (BPAgII)
 - ▲ 180 kDa, type XVII collagen
 - ▲ Transmembranous protein with a collagenous extracellular domain
 - Direct immunofluorescence (DIF) (Fig. 7-2)
 - Optimal location for DIF testing is normal-appearing perilesional skin
 - False-negative results can be observed when it is performed on lesional skin
 - Linear band of C3 (90% to 100% of patients) and IgG (70% to 90% of patients) at basement membrane zone (BMZ)
 - DIF on salt-split skin reveals IgG deposition on the blister roof
 - Indirect immunofluorescence (IIF)
 - Circulating IgG to BMZ in 70% to 80% of patients
 - Serum levels of autoantibodies against BPAgII (BP180) correlate with disease activity
- Prognosis
 - Generally, a self-limited disease with good prognosis

- Fifty percent enter remission within 2 to 6 years
- Therapy: topical steroids or oral prednisone alone or in combination with tetracycline and nicotinamide, azathioprine, cyclophosphamide, dapsone, methotrexate, plasmapheresis, and intravenous immunoglobulin (IVIG)

Cicatricial Pemphigoid (Fig. 7-3)

- Clinical
 - Erosive lesions of the skin and mucous membranes
 - Skin involvement occurs in one-third of patients
 - Usually on scalp, face, and upper trunk
 - Heals with scars
 - Bullae are tense and located on an erythematous or urticarial base
 - Bullae often occur in the same places even after temporary resolution
 - Mucosal involvement
 - Oral mainly; may present with hoarseness or dysphagia
 - Can include the nasopharynx, larynx, esophagus, genitalia, and rectal mucosa
 - May lead to esophageal stenosis requiring dilatation procedures
 - Ocular lesions
 - ▲ Characterized by chronic conjunctivitis progressing to keratinization of the corneal epithelium
 - ▲ Progressive corneal injury secondary to trichiasis (ingrown eyelashes)
 - ▲ Decreased vision, photosensitivity, and scarring (symblepharon) that eventually can cause blindness
- Brunsting-Perry variant (Fig. 7-4)
 - Variant of cicatricial pemphigoid without mucosal involvement

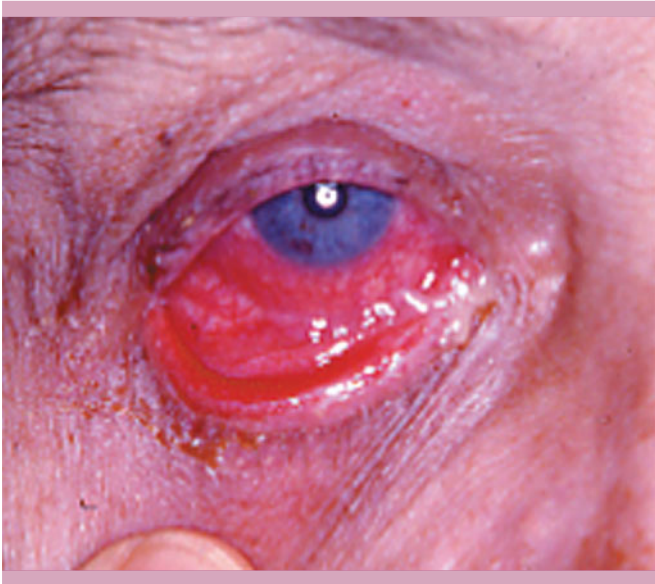


FIGURE 7-3 Cicatricial pemphigoid. (Courtesy of Dr. Robert Jordon.)

- Small blisters or erosions that heal with scarring
- Head and neck area, scalp typically involved; often occurs in older men
- Diagnosis
 - Histology
 - Blisters are subepidermal with a mixed inflammatory cell infiltrate
 - Often lesions demonstrate underlying dermal fibrosis (scar)
 - Antigens
 - Bullous pemphigoid antigen 2 (BPAG2)
 - Bullous pemphigoid antigen 1 (BPAG1)
 - B4 integrin—pure ocular form
 - Epiligrin (laminin-5) or the EBA antigen (type VII collagen)
 - Direct immunofluorescence (DIF)
 - Biopsy unaffected and perilesional skin
 - Reveals linear deposition of C3 and IgG continuously along the basement membrane
 - IgA and IgM also may be detected
 - Indirect immunofluorescence (IIF)
 - Assay reveals circulating IgG in 20% of patients, typically at low titer
 - Antiepiligrin cicatricial pemphigoid circulating autoantibodies bind to the floor of salt-split skin
 - Patients with cicatricial pemphigoid associated with reactivity to BPAG2 binding to the epidermal roof
- Course
 - Chronic progressive
 - Waxing and waning disease activity

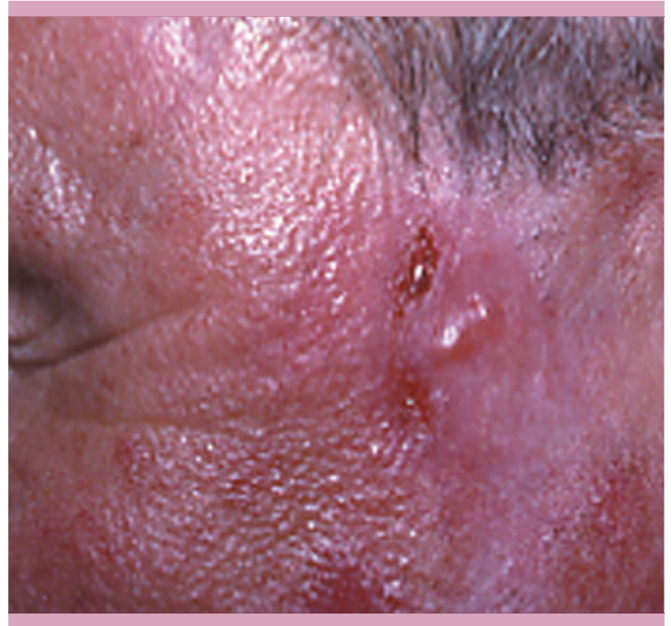


FIGURE 7-4 Cicatricial pemphigoid Brunsting-Perry. (Courtesy of Dr. Robert Jordon.)

- Sometimes CP can be a paraneoplastic condition
- Therapy
 - Topical glucocorticoids
 - Oral prednisone alone or in combination with tetracycline, azathioprine, cyclophosphamide, dapsone, methotrexate, plasmapheresis, and IVIG

Bullous Lupus Erythematosus

- Clinical
 - Blistering in the setting of the autoimmune disease systemic lupus erythematosus (SLE)
 - May coincide with the activity of the patient's preexisting SLE or may be the initial presenting cutaneous eruption of SLE
 - Patients may exhibit any of the symptoms associated with SLE
 - Extensive vesiculobullous eruption develops suddenly
 - Arises either on erythematous areas or on clinically normal skin
 - Bullae are tense and range from herpetiform vesicles to large hemorrhagic bullae
 - Not associated with skin fragility or healing of lesions with scars and milia
 - Tends to favor the upper part of the trunk and the proximal upper extremities
- Antigens: noncollagenous domain of type VII collagen (similar to patients with epidermolysis bullosa acquisita)
- Histology
 - Subepidermal separation
 - Neutrophil-predominant inflammatory infiltrate in the upper dermis

- Perivascular lymphocytic or mixed infiltrate
- Thickened and hyalinized BMZ
- Vacuolar degeneration of basal keratinocytes
- Direct immunofluorescence (DIF)
 - Perilesional skin
 - Deposition of IgG/C3 in a linear, but also a coarse and granular pattern along BMZ, often with similar deposition of IgM, IgA, and C1q (a positive “lupus band”)
 - Salt-split skin: deposition of immunoreactants on the floor of the blister cavity
- Indirect immunofluorescence (IIF): subdivided immunohistologically into type 1 and type 2 depending on the presence or absence, respectively, of identifiable circulating and/or tissue-bound antibodies to type VII collagen
- Course: bullous SLE often remits spontaneously, sometimes in less than 1 year
- Therapy
 - Dapsone
 - Systemic steroids
 - Hydroxychloroquine
 - Azathioprine
 - Methotrexate
 - Cyclophosphamide

Herpes Gestationis (Pemphigoid Gestationis) (Fig. 7-5)

- Clinical
 - Rare autoimmune dermatosis of pregnancy (1 in 50,000–60,000 pregnancies in the United States)
 - No relationship to the herpesvirus infection



FIGURE 7-5 Herpes gestationis. (Courtesy of Dr. Robert Jordon.)

- Usually occurring during second and third trimesters
- In 25% of patients, the lesions appear immediately after delivery
- Extremely pruritic polymorphic bullous dermatosis
- Hive-like plaques differ from true urticaria because of their relatively fixed nature
- Lesions commonly start on abdomen
- Rash spreads peripherally, often sparing the face, palms, soles, and mucous membranes
- Umbilical, whereas pruritic urticarial papules and plaques of pregnancy (PUPPP) typically spares the umbilicus
- Exacerbations immediately after delivery common
- Relapses with first few menses and reinitiation of oral contraceptives and with subsequent pregnancies
- Infants
 - Transient blistering or papular lesions (several weeks after delivery)
 - Greater incidence of premature and small-for-gestational-age babies
- Diagnosis
 - Histology
 - Subepidermal blister with an eosinophilpredominant infiltrate
 - Keratinocyte necrosis and dermal edema
 - Antigens
 - Extracellular domain of BP antigen II—180 kDa
 - ▲ Type XVII collagen
 - ▲ Transmembrane protein
 - Complement fixation assay: serum demonstrated herpes gestationis factor (“HG factor”), a heat-stable form of IgG that binds normal human complement to the BMZ of healthy human skin in a complement fixation assay
 - Direct immunofluorescence (DIF)
 - Normal skin and perilesional skin
 - Linear band of almost exclusively C3 deposited along the BMZ
 - Indirect immunofluorescence (IIF): specific for IgG in 20% of patients
- Course
 - Maternal mortality rate is unaffected
 - Regresses without scarring within days after delivery
 - May recur in subsequent pregnancies and may be precipitated by menses and the use of oral contraceptives
- Therapy
 - Goal is to control pruritus and suppress extensive blistering
 - Topical steroids and oral prednisone



FIGURE 7-6 Pemphigus vulgaris. (Courtesy of Dr. Robert Jordon.)

Pemphigus Vulgaris (Fig. 7-6)

- Clinical
 - Bullous disease involving the skin and mucous membranes
 - Fatal if not treated appropriately
 - Flaccid blisters rapidly progressing to erosions
 - Nikolsky's sign present
 - Lesions usually begin in the oral mucosa, followed by the appearance of skin lesions months later
 - Primary skin lesion is a flaccid blister that ruptures easily
 - Drug-induced pemphigus foliaceus associated with penicillamine, nifedipine, or captopril or other medications with a cysteine-like chemical structure
 - Vegetating pemphigus vulgaris is called pemphigus vegetans (Fig. 7-7)
 - Erosions caused by pemphigus vulgaris may develop excessive granulation tissue and crusting
 - Lesions in skin folds readily form vegetating granulations
 - Can be more resistant to therapy
- Antigens
 - Desmoglein 3
 - 130-kDa glycoprotein (member of cadherin supergene family)
 - Desmosomal core protein
 - Less commonly
 - Plakoglobin: 85-kDa plaque protein found in desmosomes



FIGURE 7-7 Pemphigus vegetans. (Courtesy of Dr. Robert Jordon.)

- Desmoglein 1: seen in patients with cutaneous and mucosal disease
- Histology
 - Biopsy the margin of a bulla
 - Suprabasilar blister with acantholysis, leads to “tombstone” appearance of residual keratinocytes lining BMZ
- Direct immunofluorescence (DIF) (Fig. 7-8)
 - Intercellular deposition of IgG and C3 in a net-like pattern throughout the epidermis of perilesional skin
- Indirect immunofluorescence (IIF)
 - Monkey esophagus and guinea pig esophagus can be used
 - Circulating IgG to keratinocyte cell surfaces in greater than 75% of patients with active disease
 - Titers correlate with disease activity
- Course: common cause of death is infection secondary to the immunosuppression required to treat the disease
- Therapy
 - Corticosteroids are the mainstay of treatment; prednisone (1 mg/kg per day), with or without other immunosuppressive agents

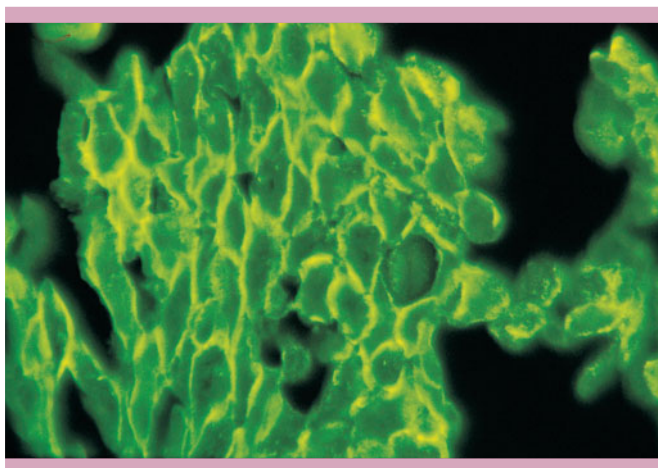


FIGURE 7-8 Pemphigus vulgaris immuno fluorescence. (Courtesy of Dr. Robert Jordon.)

- Azathioprine
- Methotrexate
- Cyclophosphamide
- Mycophenolate mofetil
- Plasmapheresis may be required in severe cases
- IVIG

Paraneoplastic Pemphigus

- Clinical
 - Tumor antigens are hypothesized to evoke an immune response that leads to the development of oral erosions or ulcerations
 - Most often related to a leukemia or non-Hodgkin lymphoma (NHL)
 - Other associated neoplasms: (malignant and benign): Waldenström's macroglobulinemia, sarcomas, thymomas, and Castleman's disease
 - Cutaneous lesions: highly variable
 - Diffuse erythema, vesiculobullous lesions, papules, scaly plaques, exfoliative erythroderma, erosions, or ulcerations
 - 100% have mucosal involvement (most often severe lingual ulceration)
- Histology
 - Biopsy from noninvolved, perilesional skin
 - Suprabasilar acantholysis with an underlying lichenoid infiltrate, basal cell vacuolation, lymphocytic exocytosis, and dyskeratotic keratinocytes with satellitosis
- Antigens
 - Desmoplakin I (250 kDa)
 - BPAG I (230 kDa)
 - Desmoplakin II (210 kDa)
 - Envoplakin (210 kDa)
 - Periplakin (190 kDa)
 - HD1/plectin (500 kDa)

- Unidentified 170-kDa protein
- Desmoglein I and desmoglein III antigens
- Direct immunofluorescence (DIF) (Fig. 7-9): IgG and C3 deposits within the intercellular spaces and along the BMZ
- Indirect immunofluorescence (IIF)
 - Positive IIF testing with rat bladder (transitional epithelium) distinguishes paraneoplastic pemphigoid from pemphigus vulgaris and pemphigus foliaceus
 - IgG autoantibodies are directed against abovementioned antigens
- Course
 - Mortality rate is estimated at 75% to 80%
 - Both the presence of an underlying neoplasm and the adverse effects of the potent medications required to treat the disease add to both the morbidity and the mortality
- Treatment: prednisone, azathioprine, cyclosporine, cyclophosphamide, rituximab (anti-CD20 antibody), IVIG

Pemphigus Foliaceus (Fig. 7-10)

- Clinical
 - Shallow, flaccid blisters rapidly progressing to scaling, crusted erosions on erythematous base
 - Localized or generalized
 - Often coalesce into large denuded areas with margined or seriginous borders
 - Rare mucous membrane involvement; sun and/or heat exacerbates disease
 - Nikolsky sign present
 - Fogo selvagem
 - Endemic pemphigus foliaceus
 - Occurs along Amazon river basin
 - Possible relation to bite of black fly *Simulium nigrimanum*
 - More common in children than nonendemic pemphigus foliaceus
- Pemphigus erythematosus (Senear and Usher)
 - Localized form of pemphigus foliaceus
 - Starts as erythematous patches with vesiculation
 - On the cheeks and forehead, with similar patches on the sternal and interscapular skin
 - May have positive antinuclear antibody (ANA) but rarely concomitant lupus erythematosus
 - Can generalize to pemphigus foliaceus
 - Crusted plaques may appear in the healing phase
- Antigens
 - Desmoglein 1
 - 160 kDa
 - Transmembrane glycoprotein of desmosomes

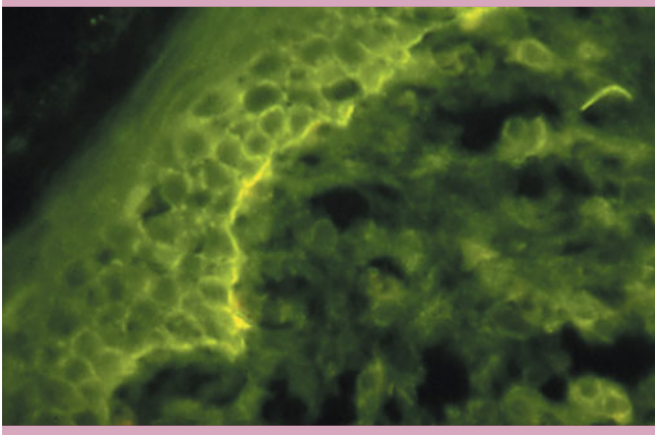


FIGURE 7-9 Paraneoplastic pemphigus immuno fluorescence. (Courtesy of Dr. Robert Jordon.)

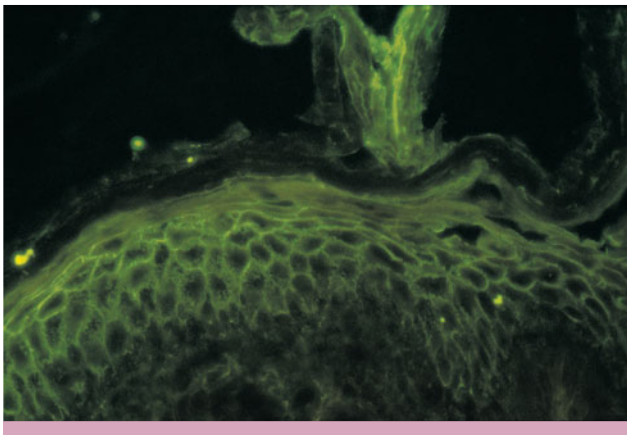
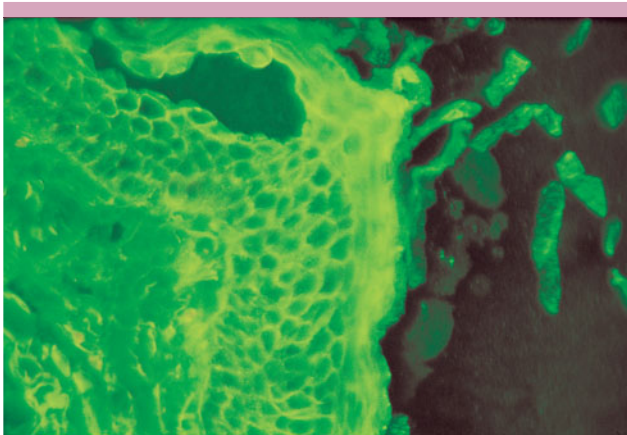


FIGURE 7-10 Pemphigus foliaceus. (Courtesy of Dr. Robert Jordon.)

- Member of cadherin superfamily
- Expressed mainly in the granular layer of the epidermis
- Plakoglobin—85-kDa desmosomal plaque protein
- Histology



FIGURE 7-11 Dermatitis herpetiformis. (Courtesy of Dr. Robert Jordon.)

- Intraepidermal acantholysis and vesiculation occurring just below stratum corneum and within the granular layer
- Full thickness acantholysis may be present in the epidermis
- Dermal lymphocytic infiltrate occurs, often with the presence of eosinophils
- Direct immunofluorescence (DIF)
 - Typically cannot distinguish with certainty from pemphigus vulgaris, although in pemphigus foliaceus the deposition of immunoreactants tends to be accentuated in the upper epidermis
 - Intercellular IgG and C3 in a net-like pattern
- Indirect immunofluorescence (IIF): guinea pig esophagus
- Therapy
 - Topical glucocorticosteroids
 - Immunosuppressants, including systemic corticosteroids, cyclophosphamide, and cyclosporine; plasmapheresis in patients with recalcitrant disease

Dermatitis Herpetiformis (Fig. 7-11)

- Associated with HLA B8-DR3-DQ2
- Clinical

- Intensely pruritic, chronic skin disease
- Onset tends to be between 20 and 40 years of age but may occur at any age, including childhood
- Intensely pruritic, chronic, grouped papules/vesicles giving a “herpetiform” appearance
- Symmetrically distributed on extensor surfaces, as well as buttocks, posterior hairline and nuchal areas
- Oral lesions rare
- Eruption commonly preceded by burning or itching
- Associated with a gluten (wheat, barley, rye \pm oats)–sensitive enteropathy
- Can lead to steatorrhea, abnormal D-xylose absorption, and anemia
- NSAIDs and iodine can induce eruptions
- Patients with increased incidence of other autoimmune disorders: thyroid disease, type 1 diabetes mellitus, systemic lupus erythematosus, vitiligo, and Sjögren’s syndrome
- Antigenes
 - IgA antibodies to gliadin (a portion of wheat protein), reticulum, and smooth muscle endomysium
 - IgA antiendomysial antibodies (tissue transglutaminase antibodies) that bind to intermyofibril substance in smooth muscle cells correlate with severity of intestinal disease and adherence to gluten-free diet
 - IgA endomysial antibodies are most specific for gluten sensitivity
 - Found in patients with dermatitis herpetiformis and those with isolated gluten sensitive enteropathy
- Histology
 - Subepidermal blister at level of lamina lucida
 - Neutrophilic microabscesses within dermal papillae, sometimes with fibrin deposition
- Direct immunofluorescence (DIF) (Fig. 7-12)
 - Granular IgA1 deposits in dermal papillae of lesional and non-lesional skin
 - Deposition of immunoreactants disappears with adherence to a gluten-free diet, but does not disappear with dapsone
- Course
 - Disease persists indefinitely
 - Waxes and wanes without treatment
- Therapy
 - Dapsone or sulfapyridine (does not treat the gastrointestinal symptoms)
 - Gluten-free diet: protein present in barley, rye, and wheat but not in rice
 - Avoid iodine and NSAIDs
 - Several studies have shown an increased incidence of GI lymphoma in dermatitis herpetiformis (similar to that of celiac disease) that is mitigated by a gluten-free diet but not from medical management

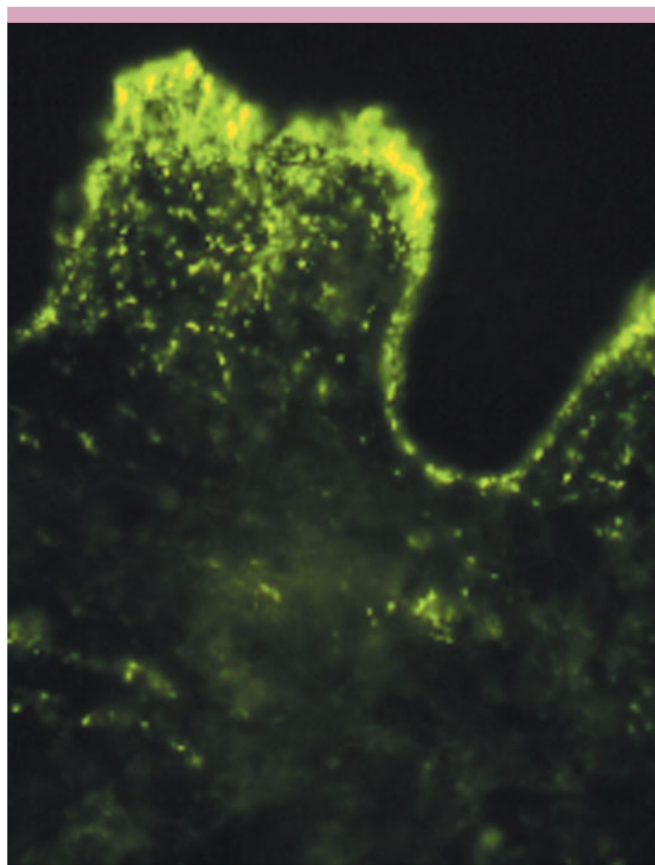


FIGURE 7-12 Dermatitis herpetiformis immuno fluorescence. (Courtesy of Dr. Robert Jordon.)

Linear IgA Dermatoses/Chronic Bullous Disease of Childhood (Fig. 7-13)

- Clinical
 - Linear IgA dermatosis
 - Most commonly presents in patients older than 30 years of age
 - Annular or grouped papules, vesicles, and/or bullae symmetrically distributed on extensor surfaces: “cluster of jewels”
 - Most commonly involves perioral/perineal areas
 - Lesions may be clinically indistinguishable from dermatitis herpetiformis
 - Seventy percent have oral involvement
- Chronic bullous disease of childhood
 - Occurs in young children, usually presenting in those younger than 5 years of age
 - Abrupt onset of tense bullae on an inflamed, erythematous base
 - Oral ulcers are noted in 50%
 - Characteristic “collarettes” of blisters often form as new lesions arise in the periphery of old lesions
- Drug associations: vancomycin, lithium, diclofenac



FIGURE 7-13 Chronic bullous disease of childhood. (Reprinted from Freedberg IM et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008, p.488)

- Antigenes
 - 97-kDa extracellular portion of BP antigen II
 - 120-kDa antigen also described
 - 97- and 120-kDa antigens may represent cleaved fragments of BPagII
- Histology
 - Subepidermal vesiculation
 - Collections of neutrophils along the basement membrane
- Direct immunofluorescence (Fig. 7-14): IgA in a linear pattern is noted along the basement membrane (occasionally IgG and C3)
- Course
 - Variable and unpredictable
 - Disease may remit spontaneously in some cases
 - May last for years with few episodes of remission in chronic bullous disease of childhood
 - Resolution occurring within 2 years of onset in most cases
- Treatment: dapsone or sulfapyridine

Epidermolysis Bullosa Acquisita (EBA)

- Clinical
 - Chronic autoimmune subepidermal blistering disease
 - Primarily involves the skin, but it also can affect mucous membranes

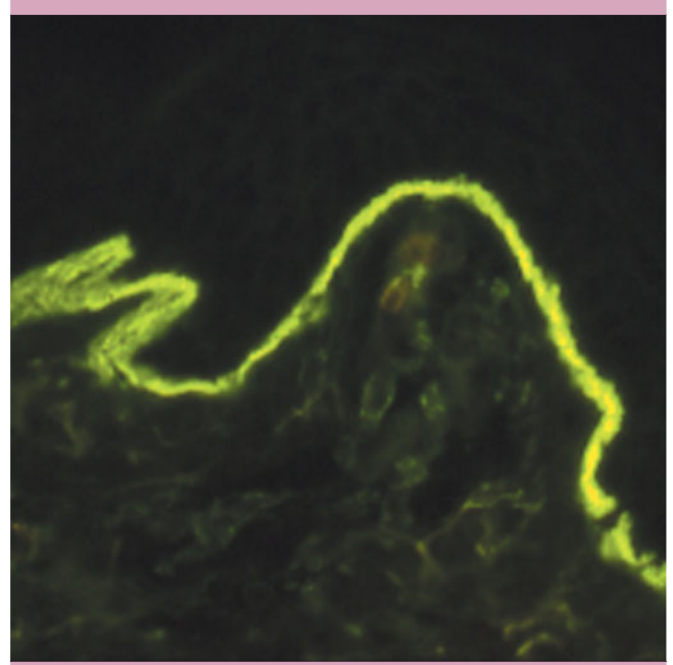


FIGURE 7-14 Linear IgA immunofluorescence. (Courtesy of Dr. Robert Jordon.)

- Trauma-prone areas of the skin: extensor surfaces of elbows, knees, ankles, and buttocks most commonly
- Bullous areas heal with scarring and formation of milia
- Nail destruction and hair loss
- Oropharyngeal mucous membrane involvement: periodontal disease, oral mucosal erosions
- Antigen: IgG autoantibodies targeting the noncollagenous (NC1) domain of type VII collagen
- Histology
 - Biopsy from edge of a new blister
 - Subepidermal blister, usually pauci-inflammatory
- Direct immunofluorescence
 - Thick band of IgG and to a lesser extent C3 deposited linearly at the BMZ
 - Salt-split skin: deposition of immunoreactants on the floor
- Indirect immunofluorescence: IgG circulating autoantibodies in the patient's serum that target the skin basement membrane component, type VII collagen
- Course: chronic inflammatory disease with periods of partial remissions and exacerbations
- Treatment: oral corticosteroids and immunosuppressants, including systemic corticosteroids, cyclophosphamide, and cyclosporine; plasmapheresis in patients with recalcitrant disease

Inherited Epidermolysis Bullosa

- See Tables 7-1 to 7-3

TABLE 7-1 Revised Classification of Inherited Epidermolysis Bullosa, Based on Clinical Phenotype and Genotype, for the Most Commonly Observed and Well-Characterized Variants or Subtypes of This Disease

Major EB Type	Major EB Subtype	Protein/Gene Systems Involved
EBS (“epidermolytic EB”)	EBS-WC	K5, K14
	EBS-K	K5, K14
	EBS-DM	K5, K14
	EBS-MD	Plectin
JEB	JEB-H	Laminin-5*
	JEB-nH	Laminin-5; type XVII collagen
	JEB-PA [†]	$\alpha_6\beta_4$ Integrin [‡]
DEB (“dermolytic EB”)	DDEB Type VII	Collagen
	RDEB-HS	Type VII collagen
	RDEB-nHS	Type VII collagen

DDEB, dominant dystrophic EB; *EBS-DM*, EBS, Dowling-Meara; *EBS-K*, EBS, Köbner; *EBS-MD*, EBS with muscular dystrophy; *EBS-WC*, EBS, Weber-Cockayne; *JEB-H*, JEB, Herlitz; *JEB-nH*, JEB, non-Herlitz; *JEB-PA*, JEB with pyloric atresia; *RDEB-HS*, recessive dystrophic EB, Hallopeau-Siemens; *RDEB-nHS*, RDEB, non-Hallopeau-Siemens.

* Laminin-5 is a macromolecule composed of 3 distinct (α_3 , β_3 , γ_2) laminin chains; mutations in any of the encoding genes result in a JEB phenotype.

[†] Some cases of EB associated with pyloric atresia may have intraepidermal cleavage or both intralamina lucida and intraepidermal clefts.

[‡] $\alpha_6\beta_4$ Integrin is a heterodimeric protein; mutations in either gene have been associated with the JEB-PA syndrome.

TABLE 7-2 Genetic Modes of Transmission in Inherited Epidermolysis Bullosa*

Major EB Type	Usual Mode(s) of Transmission	Rare Modes of Transmission
EBS [†]	Autosomal dominant	Autosomal recessive
JEB	Autosomal recessive	—
DEB	Autosomal dominant	Autosomal dominant/autosomal recessive heterozygosity
	Autosomal recessive	

* Excluding de novo mutations, which have been reported to occur in most forms of inherited EB.

[†] An X-linked recessive disorder, referred to as Mendes da Costa disease, which was once included among the many variants of EBS, is no longer considered to be a subtype of any form of inherited EB.

TABLE 7-3 Ultrastructural Findings Among Major Types and Selected Subtypes of Inherited Epidermolysis Bullosa

EB Type or Subtype	Ultrastructural Site of Skin Cleavage	Other Ultrastructural Findings
EBS		
EBS-WC	Intrastratum basale	Split may spread to the suprabasilar layer
EBS-DM	Intrastratum basale, just superficial to the HD	Dense, circumscribed clumps of keratin filaments (most commonly observed within lesional biopsy sites)
EBS-MD	Predominantly in the stratum basale, above the level of the HD attachment plaque	Lack of integration of keratin filaments with HD
EBS-AR	Intrastratum basale	Absent keratin filaments within basal keratinocytes
EBSS	Intrastratum granulosum	—
JEB		
JEB-H	Intralamina lucida	Markedly reduced or absent HD; absent SBDP
JEB-nH	Intralamina lucida	Variable numbers or rudimentary appearance of HDs
JEB-PA	Both intralamina lucida and lower stratum basale, above the level of the HD plaque	Small HD plaques often with attenuated SBDP, and reduced integration of keratin filaments with HD
DDEB		
DDEB	Sublamina densa	Normal or decreased numbers of AF
DDEB-TBDN	Sublamina densa	Electron-dense stellate bodies within stratum basale; reduced AF
RDEB		
RDEB-HS	Sublamina densa	Absent AF
RDEB-nHS	Sublamina densa	Reduced or rudimentary-appearing AF

AF, anchoring fibril; HD, hemidesmosome; SBDP, subbasal dense plate; for explanation of other abbreviations, see footnote to Table 7-1.

Modified from Fine J-D, Smith LT: Non-molecular diagnostic testing of inherited epidermolysis bullosa: current techniques, major findings, and relative sensitivity and specificity, in Fine J-D, Bauer EA, McGuire J, Moshell A, eds. *Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry*. Baltimore: Johns Hopkins University Press; 1999, p. 52.

QUIZ

Questions

- All of the following are true of bullous pemphigoid *EXCEPT*:
 - It is most common in patients older than 60 years
 - It is a subepidermal vesiculatory process
 - It involves the oral mucosa in a majority of cases
 - Patients often suffer from other co-morbidities
 - Urticarial forms may predate formation of frank blisters
- In bullous pemphigoid, DIF examination of perilesional skin most often demonstrates:
 - IgA deposition in a linear band along the dermoepidermal junction
 - IgA deposition in a granular pattern within the papillary dermis
 - IgG accumulation in a net-like pattern in the epidermis
 - IgG accumulation in a linear band along the dermoepidermal junction
 - C3 accumulation in a granular pattern along the dermoepidermal junction
- The Brunsting-Perry variant of cicatricial alopecia involves the:
 - Acral skin
 - Conjunctiva
 - Oral mucosa
 - Scalp
 - All of the above
- DIF examination of salt-split skin demonstrates deposition of immunoreactants along the *roof* of the blister cavity in:
 - Anti-epiligrin cicatricial pemphigoid
 - Bullous pemphigoid
 - Bullous lupus erythematosus
 - Epidermolysis bullosa acquisita
 - Epidermolysis bullosa simplex
- Histologic and immunofluorescence findings in dermatitis herpetiformis may include:
 - Accumulation of neutrophils in the papillary dermis
 - Fibrin deposition in the papillary dermis
 - Granular IgA deposition in the papillary dermis
 - Subepidermal vesiculation
 - All of the above
- A gluten-free diet, used to manage dermatitis herpetiformis, can safely include cereal or grain products derived from:
 - Barley
 - Rice
 - Rye
 - Triticale
 - Wheat
- DIF examination of perilesional tissue involved with pemphigus vulgaris reveals deposition of:
 - IgA in a linear pattern along the dermoepidermal junction
 - IgA in a granular pattern along the dermoepidermal junction
 - IgG in a linear pattern along the dermoepidermal junction
 - IgG in a net-like pattern within the dermis
 - IgG in a net-like pattern within the epidermis
- Pemphigus foliaceus is characterized by antibodies to:
 - Desmocollin 1
 - Desmocollin 3
 - Desmoglein 1
 - Desmoglein 3
 - Desmoplakin
- By definition, paraneoplastic pemphigus always involves the _____.
 - Acral surfaces
 - Conjunctiva
 - Oral mucosa
 - Scalp
 - Skin
- Patients with bullous systemic lupus erythematosus and epidermolysis bullosa acquisita both may demonstrate antibodies to:
 - BPAg I (230 kD)
 - BPAg II (180 kD)
 - Collagen VII
 - Desmoglein 1
 - Desmoglein 3

Answers

- C. Patients with bullous pemphigoid are typically older (> 60 years old) with co-morbidities. Unlike pemphigus, most cases of bullous pemphigoid do not involve the mucosa. Urticarial bullous pemphigoid may predate development of frank blisters, sometimes by years. Bullous pemphigoid is a subepidermal vesiculatory process.
- D. In bullous pemphigoid, DIF examination most often reveals linear deposition of C3 (90–100%) and IgG (70–90%) along the dermoepidermal junction. While C3 deposition is even more common

- than IgG deposition in bullous pemphigoid, it is linear and not coarse and granular.
3. D. The Brunsting-Perry variant of cicatricial pemphigoid most often affects the scalp of elderly men. It is distinguished from other variants of cicatricial pemphigoid because it does *NOT* involve the mucosa.
 4. B. Because cleavage occurs through the lamina lucida, DIF examination of salt-split skin from bullous pemphigoid demonstrates deposition of immunoreactants on the roof of the blister cavity. For all the other immunobullous diseases, salt-split DIF examination would result in deposition of immunoreactants in the floor of the cavity. Epidermolysis bullosa simplex is not an acquired immunobullous disorder, but a genetic bullous disorder.
 5. E. Dermatitis herpetiformis demonstrates subepidermal vesiculation and an accumulation of neutrophils and fibrin in the papillary dermis. DIF demonstrates granular deposition of IgA in lesional and non-lesional skin, but it may disappear during strict adherence to a gluten-free diet.
 6. B. Rice contains no gluten. The other grains contain gluten. The presence of gluten in oats is both variable and controversial, and it may depend upon processing techniques.
 7. E. Pemphigus vulgaris and pemphigus foliaceus demonstrate deposition of IgG and C3 in a net-like pattern within the epidermis. Hence, these diseases are suprabasilar immunobullous conditions.
 8. C. Pemphigus foliaceus is characterized by antibodies to desmoglein 1 (160 kD). The desmocollins are believed to play a role in subcorneal pustular dermatosis and possibly IgA pemphigus. Antibodies to desmoplakin are involved in paraneoplastic pemphigus.
 9. C. Paraneoplastic pemphigus always involves the oral mucosa, usually with severe ulcerations of the tongue. In fact, severe painful stomatitis is one of the diagnostic criteria for the disease.
 10. C. Patients with bullous systemic lupus erythematosus and epidermolysis bullosa acquisita may both demonstrate antibodies to collagen VII, a constituent of the anchoring fibrils of the skin.

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DISORDERS OF CORNIFICATION, INFILTRATION, AND INFLAMMATION

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CUTANEOUS DISORDERS OF CORNIFICATION

Icthyoses

- Group of disorders characterized by generalized scaling of the skin
- Pathogenesis: increased cohesiveness of cells of the stratum corneum, abnormal keratinization, and abnormal proliferation

ICTHYOSIS VULGARIS (FIG. 8-1)

- Epidemiology: most common disorder of cornification; AD
- Pathogenesis
 - Loss of function mutation in filaggrin (FLG) gene
 - Increased adherence of the stratum corneum and scale formation is thought to result from a lack of water-retaining amino acids that derive from filaggrin metabolism
- Clinical features
 - Not present at birth; onset during infancy/childhood
 - Fine white, flaky scales develop on the extremities, especially the extensor surfaces with sparing of the groin and flexural areas due to increased humidity
 - Improves with advancing age
 - Associated with keratosis pilaris and atopic triad of asthma, hay fever and eczema
- Pathology
 - One-half lack granular layer on light microscopy and profilaggrin-containing keratohyalin granules by EM

- Treatment
 - Lubricants and emollients
 - Keratolytics—be careful with salicylic acid to avoid salicylism
 - Topical retinoids – can be irritating

LAMELLAR ICTHYOSIS (FIG. 8-2)

- Epidemiology: AR
- Pathogenesis
 - In the majority of patients, it is caused by transglutaminase-1 deficiency due to mutations in the TGM1 gene
 - Has also been mapped to the ATP binding cassette transporter gene (ABCA12) and the cytochrome P450 family 4, subfamily F, polypeptide 22 gene (CYP4F22)
- Clinical features
 - Apparent at birth and persists throughout life
 - Collodion baby
 - Characterized by large, dark-brown and plate-like scales that form a mosaic pattern with minimal to no erythroderma
 - Ectropion, eclabium and significant hypoplasia of nasal and auricular cartilage due to tautness of facial skin
 - Variable PPK, may have alopecia and nail dystrophy
- Treatment
 - Oral retinoids may be necessary from early childhood if severe
 - Keratolytics limited secondary to irritation and systemic absorption



FIGURE 8-1 Ichthyosis vulgaris. (Reprinted with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003, p. 487.)

- Topical vitamin D3 derivatives
- Palliation for heat intolerance
- Ophthalmology follow up

NON-BULLOUS CONGENITAL ICTHYOSIFORM ERYTHODERMA

- Epidemiology: AR
- Pathogenesis
 - Mapped to four different genes: transglutaminase 1, ALOXE3, ALOX12B, ichthyin
 - 12-LOX generates fatty acid hydroperoxide, eLOX functions as hydroperoxide isomerase to generate epoxy alcohols
- Clinical features
 - Presents at birth with a collodion membrane which persists throughout life
 - Characterized by intense erythroderma, white small powdery scale, ectropion and scarring alopecia
 - Palms and soles have diffuse, fissuring keratoderma
 - Obstruction of sweat ducts and pores results in hypohidrosis and heat intolerance
- Pathology
 - Increased lamellar bodies, accumulation of lipid droplets in the stratum corneum
- Treatment
 - See lamellar ichthyosis
 - Erythrodermic patients need supplemented fluid, calories, iron and protein to balance increased loss through the skin



FIGURE 8-2 Lamellar ichthyosis. (Reprinted with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003, p. 490.)

X-LINKED ICTHYOSIS

- Epidemiology: XLR; affects males almost exclusively
- Pathogenesis
 - Decreased or absent steroid sulfatase activity
 - Results in impaired hydrolysis of cholesterol sulfate and DHEA-S with subsequent accumulation of cholesterol 3-sulfate in the epidermis, which may inhibit TGM-1
- Clinical features
 - In women pregnant with an affected fetus, steroid sulfatase deficiency in the fetal placenta causes low or absent levels of estrogen, which causes failure of progression of labor
 - Presents within first weeks after birth with mild erythroderma and generalized peeling of large, translucent scale
 - The typical large, polygonal, dark-brown scale with tight adherence develops during infancy and is distributed on the extremities, trunk and neck
 - Palms, soles and face spared—except pre-auricular areas
 - Asymptomatic corneal opacities in 10–50%
 - 20 fold increase of cryptorchidism and testicular cancer and hypogonadism
- Treatment
 - Emollients
 - Topical keratolytics
 - Topical retinoids

ICTHYOSIS BULLOSA OF SIEMENS

- Epidemiology: AR
- Pathogenesis: heterozygous mutations in gene for keratin 2—expressed in uppermost spinous and granular cell layers of the epidermis
- Clinical features
 - At birth—may appear normal or show mild blistering
 - Trauma induced blistering in infancy
 - Hyperkeratosis develops in early childhood
 - Predilection for skin overlying joints, flexures and dorsa of hands/feet—spares palms and soles
 - Characteristic feature is superficially denuded areas with collarette-like borders
- Pathology: clumping of tonofilaments on EM
- Treatment: see bullous CIE

BULLOUS CONGENITAL ICTHYOSIFORM ERYTHRODERMA

- Epidemiology: AD; ~ 50% occur sporadically (new mutations)
- Pathogenesis
 - Heterozygous mutations in keratins 1 and 10, which are expressed in the suprabasal and granular layers of the epidermis
 - KRT1 is associated with severe PPK

- KRT10 spares the palms/soles—not expressed there
- Epidermal acantholysis and hyperkeratosis result from hyperproliferation, decreased desquamation and other factors
- Clinical features
 - Presents at birth with erythroderma, erosions, peeling and widespread areas of denuded skin
 - Over time, blistering and erythroderma resolve and hyperkeratosis prevails
 - Increased transepidermal water loss and bacterial colonization of the stratum corneum due to disturbed barrier function
 - Sepsis and fluid and electrolyte imbalances account for perinatal morbidity and mortality
- Pathology: epidermolytic hyperkeratosis—massive, dense orthokeratotic hyperkeratosis, acanthosis with hypergranulosis and cytolysis of the suprabasal and granular layers
- Treatment
 - NICU during neonatal period
 - Keratolytics—limited due to irritation and salicylism
 - Topical emollients, tretinoin and vitamin D
 - Antibiotics as needed for bacterial infection; antiseptics or antibacterial soaps
 - Systemic retinoids

ICTHYOSIS HYSTRIX CURTH-MACKLIN

- Epidemiology: AR
- Pathogenesis: mutations in the keratin 1 gene
- Clinical features
 - No skin fragility
 - Ranges from severe, mutilating PPK to generalized hystrix-like hyperkeratosis
 - Pseudoainhum, starfish-like hyperkeratoses, knuckle pads, flexural digital contractures and secondary bacterial infections have been described
- Treatment: systemic retinoids and topical keratolytic agents
- Ichthyosis hystrix—descriptive name for a clinically and genetically heterogeneous group of skin disorders with massive hyperkeratosis that has a verrucous surface or protruding, porcupine-like spines

HARLEQUIN FETUS

- Epidemiology: AR
- Pathogenesis
 - Massive cell retention in the stratum corneum, abnormal or absent lamellar bodies and lack of intercellular lipid lamellae
 - Loss of function mutations in the ABC transporter gene ABCA12—codes for lamellar bodies involved in energy dependent lipid transport

- Clinical features
 - Born prematurely and die within a few days or weeks after birth due to complications of prematurity, respiratory insufficiency, sepsis, hypothermia, and/or hypernatremic dehydration
 - Encased in a hard armor-like thickened stratum corneum that immobilizes the baby
 - A few days later, cracks form large, yellow, adherent plates separated by broad, deep, and intensely red fissures
 - Ectropion, eclabium and rudimentary development of ear and nasal cartilage due to tautness of skin
 - Hands/feet are edematous and swollen
 - Increased transcutaneous water loss and heat results in dehydration, electrolyte imbalance and temperature instability
 - Intelligence is usually normal
- Pathology: hair follicles show marked, concentric accumulation of keratotic material around hair shafts, which is considered a diagnostic feature
- Treatment
 - ICU care
 - Ophthalmology for severe ectropion
 - Systemic retinoids

SJÖGREN-LARSON SYNDROME

- Epidemiology: AR
- Pathogenesis: Deficiency of microsomal enzyme fatty aldehyde dehydrogenase (FALDH), which catalyzes the NAD dependent oxidation of long-chain aliphatic aldehydes
- Clinical features
 - Presents at birth with varying degrees of erythema and ichthyosis
 - Rare collodion membrane
 - After infancy, erythema fades, while hyperkeratosis and scaling become more prominent
 - Predilection sites are the lower abdomen, side and nape of neck and large flexures
 - 70% develop PPK
 - Associated with persistent pruritus
 - Presence of perifoveal glistening white dots in the ocular fundus
 - Involvement of the CNS manifests in the first year of life with delayed motor development, abnormal gait, pyramidal signs and spasticity
 - Progressive neurologic decline results in di- or tetraplegia and severe MR
- Treatment
 - Topical keratolytics and topical vitamin D
 - Skin hydration
 - Systemic retinoids
 - 5-lipoxygenase inhibitors—for pruritus
 - Symptomatic treatment for CNS effects

REFSUM DISEASE

- Epidemiology: AR
- Pathogenesis
 - Excessive accumulation of phytanic acid caused by a deficiency of peroxisomal enzyme phytanoyl-CoA hydroxylase
 - Two genes are implicated: PHYH and PEX7
 - Inactivating mutations in PHYH lead to an enzymatic block with subsequent accumulation of phytanic acid in plasma and tissues
- Clinical features
 - Cutaneous symptoms are variable and tend to develop during childhood or adolescence
 - Starts with insidious neurologic symptoms
 - Waxes and wanes with resulting gradual neurologic deterioration
 - Cardinal features are atypical retinal pigmentosa leading to concentric visual field constriction, peripheral polyneuropathy, cerebellar dysfunction and elevated protein in CSF
 - Cardiomyopathy resulting in arrhythmias, AV conduction impairment and cardiomegaly are responsible for the increased incidence of sudden death
- Pathology: diagnosis established by detecting increased phytanic acid levels in serum
- Treatment
 - Reducing dietary phytanic acid intake (in dairy products and animal fats)
 - Retinal changes are irreversible
 - Therapeutic plasma exchange may be useful for acute toxicity

NEUTRAL LIPID STORAGE DISEASE WITH ICTHYOSIS

- Epidemiology: AR
- Pathogenesis
 - Inborn error of lipid metabolism with multiorgan accumulation of triglycerides
 - Germline mutations in CGI-58 gene
- Clinical features
 - Congenital generalized ichthyosis, vacuolated leukocytes, myopathy, cataracts and sensorineural deafness
 - Widespread tissue deposition of neutral lipids results in a broad array of systemic manifestations in childhood
 - Prognosis depends on the course of liver disease and extent of hepatic fibrosis
- Pathology: Diagnostic feature is the presence of numerous lipid-containing vacuoles in circulating granulocytes (Jordan's anomaly)
- Treatment
 - Topical emollients and keratolytics

- Systemic retinoids
- Fat-restricted diets

Conradi-Hünemann Syndrome

- Epidemiology: XLD
- Pathogenesis
 - Caused by a primary defect in cholesterol biosynthesis
 - Distinct mutations in EBP gene encoding emopamil-binding protein
- Clinical features
 - Generalized erythema with thick adherent scale and linear or whorled hyperkeratosis at birth
 - Erythroderma resolves substantially or completely within first weeks/months of life
 - In older children, hyperkeratosis is replaced by linear or patchy follicular atrophoderma
 - Skeletal abnormalities are usually asymmetric
 - Widespread calcifications manifest as stippled epiphyses (chondrodysplasia punctata)—typically involves the trachea and vertebra; can be detected on radiographs in childhood, but not apparent when bone maturation progresses
 - Unilateral cataracts
 - Normal life expectancy
- Treatment
 - Emmollients, urea or lactic acid containing products
 - Orthopedic and ophthalmology consults

CHILD

- Epidemiology: XLD
- Pathogenesis: Inactivating mutation in NSDHL—encodes 3 β -hydroxysteroid-dehydrogenase
- Clinical features
 - Presents at birth or neonatal period with striking unilateral erythema and skin thickening with a waxy surface or yellowish adherent scale
 - Often involves right side of body and sharply demarcated at midline
 - Spares the face
 - Ipsilateral skeletal abnormalities range from hypoplasia of digits or ribs to complete amelia
 - Stippled epiphyses can be seen on radiographs in early infancy but resolve during childhood
 - Organ hypoplasia affects brain, kidney, heart and lungs
- Treatment
 - Multidisciplinary depending on organ involvement
 - Topical tretinoin, systemic retinoids or surgical excision

NETHERTON SYNDROME (ICTHYOSIS LINEARIS CIRCUMFLEXA)

- Epidemiology: AR

- Pathogenesis: caused by mutation in the SPINK5 gene—encodes multi-domain serine protease inhibitor LEKT1, predominantly expressed in lamellar granule system of epithelia and lymphoid tissue
- Clinical features
 - Presents at or soon after birth with generalized erythroderma and scaling
 - Collodion membrane usually not present
 - Usually, ichthyosis evolves into serpiginous or circinate scaling and erythematous plaques which are bordered by a double-edged scale
 - Hair shaft abnormalities develop during infancy and improve with age—include trichorrhexis invaginata and trichorrhexis nodosa
 - Increased levels of IgE, eosinophilia and increased allergic reactions
 - Increased susceptibility to skin, respiratory tract or systemic infections
- Treatment
 - Symptomatic
 - May require NICU
 - Topical emollients, keratolytics, tretinoin and corticosteroids
 - Avoid topical tacrolimus due to percutaneous absorption
 - Treatment of bacterial/fungal infections as needed

ERYTHROKERATODERMA VARIABIS (MENDES DE COSTA DISEASE)

- Epidemiology: AD
- Pathogenesis: Mutations in the connexin genes GJB3 & GJB4—encode gap junction proteins connexin 31 and connexin 30.3
- Clinical features
 - Hallmark is the coexistence of transient erythematous patches and more stable hyperkeratosis
 - Erythematous component more prevalent during childhood
 - Individual lesions persist for minutes to hours
 - Over time, hyperkeratosis develops
 - Stabilizes after puberty
 - May be triggered by other factors, including stress, temperature changes, friction and sun exposure
- Treatment
 - Keratolytic agents for mild disease
 - Systemic retinoids for extensive disease

KERATOSIS-ICTHYOSIS-DEAFNESS SYNDROME (KID)

- Epidemiology: AD
- Pathogenesis: Mutations in GJB2 encoding connexin 26

- Clinical features
 - First manifest with transient erythroderma at birth or infancy
 - Symmetrically distributed, well-demarcated hyperkeratotic plaques with an erythematous base and rough, ridged or verrucous surfaces that develop later
 - Stippled PPK
 - Non progressive congenital sensorineural hearing impairment—generally severe and bilateral
 - Eye symptoms manifest at birth, infancy or early childhood and worsen with age
 - Increased susceptibility to mucocutaneous bacterial, viral, and fungal infections (especially *C. albicans*)
 - SCC of the skin and oral mucosa is a serious complication that may shorten life expectancy
- Treatment
 - Emollients, keratolytics and topical retinoids
 - Mixed success with systemic retinoids—may aggravate keratitis and neovascularization
 - Hearing aids and cochlear implants have been used successfully
 - Corneal transplants are not very successful due to revascularization

Palmoplantar Keratodermas (PPKs)

UNNA THOST SYNDROME (NON-EPIDERMOLYTIC HYPERKERATOSIS)

- Epidemiology: AD
- Pathogenesis: keratin 1 mutation
- Clinical features
 - Initially erythema of palmoplantar skin with eventual thick yellow hyperkeratosis that expands to involve the lateral aspects of the hands and feet
 - Usually well developed by age 3–4
 - Non-transgradient
 - Hyperhidrosis, secondary dermatophyte infections and pitted keratolysis are common
- Treatment
 - Keratolytics
 - Mechanical debridement
 - Variable improvement with systemic retinoids

VORNER'S SYNDROME (EPIDERMOLYTIC HYPERKERATOSIS)

- Epidemiology: AD
- Pathogenesis: keratin 9 mutation
- Clinical features: see NEPPK; blisters occasionally reported
- Pathology: epidermolytic hyperkeratosis, clumped tonofilaments
- Treatment: see NEPPK

HOWEL-EVANS SYNDROME

- Epidemiology: AD; TOC gene
 - Type A—late onset PPK and increased risk of esophageal carcinoma
 - Type B—early onset PPK and benign course
- Clinical features
 - PPK often limited to pressure areas
 - Associated with keratosis pilaris, dry rough skin and oral leukokeratosis
 - Esophageal carcinoma arises in the 5th decade

VOHWINKEL SYNDROME (MUTILATING PALMOPLANTAR KERATODERMA)

- Epidemiology: AD
- Pathogenesis
 - Mutation in gene encoding loricrin, a major cornified envelope protein
 - Mutation in connexin 26
- Clinical features
 - Honeycombed, diffuse hyperkeratosis of the palms of soles that appears in infancy and becomes transgradient
 - Early childhood development of constricting bands of the digits, which may lead to autoamputation (pseudoainhum)
 - Starfish shaped keratoses over the knuckles of the fingers and toes
 - Moderate hearing loss

MAL DE MALEDA

- Epidemiology: AR; inhabitants off the Dalmatian coast
- Pathogenesis: SLURP-1 mutation
- Clinical features
 - Onset of diffuse palmar and plantar thickening with an erythematous border, shortly after birth
 - Progressive and transgradient with knee and elbow involvement
 - Severe hyperhidrosis and malodor
 - Complicated by fissuring and secondary fungal or bacterial infections

PAPILLON-LEFEVRE SYNDROME

- Epidemiology: AR
- Pathogenesis: mutations in cathepsin C
- Clinical features
 - Diffuse transgradient PPK
 - Destructive periodontitis beginning in childhood
 - Frequent cutaneous and systemic pyogenic infections

RICHNER-HANHART SYNDROME

- Epidemiology: AR
- Pathogenesis: mutations in TAT gene – encodes hepatic tyrosine aminotransferase

- Clinical features
 - Photophobia, dendritic keratitis with corneal ulcerations in the 1st year of life
 - Elevated serum and urine tyrosine levels
 - Painful, focal hyperkeratotic plaques on the palms and soles
 - Progressive mental retardation
- Treatment: diet restricted in tyrosine and phenylalanine will clear the keratitis and skin lesions and may delay or prevent cognitive impairment

BART-PUMPHREY SYNDROME

- Epidemiology: AR
- Pathogenesis: mutation in GJB2 gene that encodes connexin 26
- Clinical features
 - Profound hearing impairment from birth
 - Early childhood development of diffuse PPK (pitted or stippled) and knuckle pads
 - Variable leukonychia that improves with age

HURIEZ SYNDROME

- Epidemiology: AD
- Clinical features
 - Red, atrophic skin on the dorsal aspects on the hands and feet since birth
 - Mild and diffuse PPK
 - Sclerodactyly and nail changes with time
 - Increased risk of SCC in areas of atrophic skin
- Pathology: characteristic finding is almost complete absence of Langerhans cells in the affected skin

HIDROTIC ECTODERMAL DYSPLASIA (CLOUSTON SYNDROME)

- Epidemiology: AK
- Pathogenesis: mutations of GJB6 gene that encodes connexin 30
- Clinical features
 - Diffuse PPK in conjunction with hypotrichosis and nail dystrophy
 - Thickened skin may develop over the knuckles, knees and elbows
 - Loss of hair shaft cuticle

OLMSTED SYNDROME

- Epidemiology: AD and XLR
- Clinical features
 - Well-defined erythematous hyperkeratotic plaques in the perioral, inguinal, genital, and intergluteal areas during the 1st year of life
 - PPK that begins in infancy that becomes diffuse and severe
 - Autoamputation may result from constricting PPK and SCC or melanoma may occur

NAXOS DISEASE

- Epidemiology: AR
- Pathogenesis: deletion of the plakoglobin gene
- Clinical features: arrhythmogenic right ventricular cardiomyopathy, mild non-transgradient, non-epidermolytic PPK and wooly hair

CARVAJAL SYNDROME

- Epidemiology: AR; in 3 families from Ecuador
- Pathogenesis: mutation in gene that encodes desmoplakin
- Clinical features: striate epidermolytic PPK, left ventricular dilated cardiomyopathy and wooly hair
- Treatment: needs cardiac evaluation—as do patients with Naxos disease

DARIER DISEASE

- Epidemiology: AD; men and women equally affected
- Pathogenesis
 - Mutations in the endoplasmic reticulum Ca^{2+} ATPase ATP2A2-protein product SERCA2
 - Defects in Ca^{2+} sequestration into the endoplasmic reticulum produce acantholysis by impairing the normal processing of junctional proteins (desmoplakins)
 - Keratinocyte ER Ca^{2+} depletion is also associated with apoptosis
- Clinical features
 - Peak onset during puberty
 - Primary lesions are keratotic, red to brown papules in a seborrheic distribution, involving the trunk, scalp, face and lateral neck
 - Malodor is frequent
 - Nail changes include longitudinal red and/or white lines, longitudinal ridging, subungual hyperkeratosis and V-shaped notches
 - Worsens in summer and with lithium
 - Chronic course without spontaneous remission
 - Prone to secondary infection including bacteria, yeast, dermatophytes or Kaposi's varicelliform eruption (HSV)
- Pathology
 - Acantholysis and dyskeratosis
 - Corps ronds—acantholytic enlarged keratinocytes in malpighian layer with darkly staining and partially fragmented nuclei surrounded by a clear cytoplasm and encircled by a bright ring of collapsed keratin bundles
 - Grains—small, oval cells in the stratum corneum characterized by a strongly eosinophilic cytoplasm composed of collapsed keratin bundles containing shrunken parakeratotic nuclear remnants
- Treatment
 - Lightweight clothing and sunscreen
 - Topical retinoids and emollients

- Antimicrobial washes and intermittent use of antibiotics/antifungals
- Systemic retinoids
- Excision followed by STSG, dermabrasion or laser removal

POROKERATOSES (FIG. 8-3)

- Epidemiology: AD
- Pathogenesis: clonal hyperproliferation of atypical keratinocytes: causes cornoid lamella, which expands peripherally and forms the raised boundary between abnormal and normal keratinocytes
- Clinical features: five clinical variants
 - Classic porokeratosis Mibelli
 - Childhood, asymptomatic
 - Irregularly shaped annular plaque with a raised, ridgelike border
 - Sex predominance: M: F 2:1 to 3:1
 - Few lesions
 - Mucous membrane involved
 - Localized, anywhere
 - Koebner phenomenon reported
 - Disseminated superficial porokeratosis (DSP) and disseminated superficial actinic porokeratosis (DSAP)
 - Indistinct, light brown patches with a thread-like border
 - Predominantly on the extensor surfaces of the legs and the arms
 - Fair-skinned women in their third or fourth decade of life, with a history of excessive ultraviolet exposure (DSAP)
 - Sex predominance: M:F 1:3
 - Linear porokeratosis
 - Infancy or early childhood
 - Inheritance: unknown
 - Unilateral, linear array of annular papules and plaques with the characteristic raised peripheral ridge
 - Follows a dermatomal distribution
 - Sex predominance: M:F 1:1
 - Porokeratosis palmaris et plantaris disseminata (PPPD)
 - Small, slightly hyperpigmented, atrophic center, and a minimally raised peripheral ridge
 - Mucosal lesions are small, annular or serpiginous, and pale
 - Palms and the soles, then generalized distribution
 - Sex predominance: M:F 2:1
- Pathology
 - Cornoid lamella: thin column of tightly packed parakeratotic cells within a keratin-filled epidermal invagination; extends at an angle away from the center of the lesion
 - Epidermis, beneath the parakeratotic column, has keratinocytes that are irregularly arranged with atypical nuclei
 - Papillary dermis with a moderately dense lymphocytic infiltrate and dilated capillaries
- Treatment
 - Topical 5-fluorouracil, topical vitamin D₃ analogues, oral retinoids; excision if malignancy occurs
 - Cryotherapy electrodesiccation and curettage
 - Therapeutic measures that might increase the malignant potential, such as irradiation, immunosuppression, and excessive UV exposure, should be avoided



FIGURE 8-3 Porokeratosis. (Courtesy of Dr. Asra Ali.)

Pityriasis Rubra Pilaris (PRP)

- Epidemiology: AD
- Pathogenesis: vitamin A deficiency and abnormal vitamin A metabolism
- Clinical features
 - Rare, onset at any age, chronic course
 - Both sexes equally affected
 - Orange-red or salmon-colored scaly plaques with sharp borders, islands of uninvolved skin
 - Juvenile, adult, limited forms
 - Tendency for erythroderma
 - Follicular hyperkeratosis
 - Palmoplantar keratoderma
 - Nails: distal yellow-brown discoloration, subungual hyperkeratosis, longitudinal ridging, nail plate thickening, and splinter hemorrhages
 - Mucous membrane: diffuse whitish appearance of the buccal mucosa, lacy whitish plaques, and erosions

- Griffith's classification
 - Type I: classic adult, most common and good prognosis
 - Type II: atypical adult
 - Type III: classic juvenile, most common and good prognosis
 - Type IV: circumscribed juvenile
 - Type V: atypical juvenile
 - Type VI: HIV-associated
- Pathology
 - Hyperkeratosis with alternating orthokeratosis and parakeratosis forming a checkerboard pattern in the stratum corneum
 - Focal or confluent hypergranulosis; follicular plugging with perifollicular parakeratosis forming a shoulder effect;
 - Thick suprapapillary plates; broad rete ridges; narrow dermal papillae; and sparse superficial dermal lymphocytic perivascular infiltration, acantholysis
- Treatment: topical corticosteroids, calcipotriol, emollients, acitretin, methotrexate, azathioprine

Lichen Simplex Chronica (Fig. 8-4)

- Epidemiology
 - Older adults
- Pathogenesis
 - Secondary to habitual scratching/rubbing of skin



FIGURE 8-4 Lichen simplex. (Courtesy of Dr. Asra Ali.)

- Linked to obsessive-compulsive disorder (OCD)
- Predisposing factors: xerosis, atopy
- Clinical features
 - Hyperpigmented, lichenified, well-circumscribed leathery plaques
 - Common distribution
 - Women: occipital/nuchal areas
 - Men: perineum/scrotum
 - Wrists, extensor forearms, lower legs
- Pathology
 - Hyperkeratosis, acanthosis, hypergranulosis, fibrosis and increased number of dilated capillaries
 - Sometimes excoriations are found
- Treatment
 - Break the itch-scratch cycle
 - Anti-pruritics/moisturizers
 - Topical corticosteroids under occlusion
 - Intralesional corticosteroids
 - Reduce situational stressors/counseling/support groups
 - SSRIs = in patients with OCD

Tyloma (Callus)

- Pathogenesis
 - Caused by chronic external pressure
- Pathology
 - Prominent hyperkeratosis, usually without parakeratosis

Clavus

- Pathogenesis
 - Caused by chronic pressure at the site of bony prominences
- Clinical findings
 - Hyperkeratotic lesion
- Pathology
 - Hyperkeratosis with parakeratosis
 - Epidermis is centrally atrophic and peripherally acanthotic
 - Perivascular infiltration of upper dermis

Pityriasis Lichenoides (Fig. 8-5)

- Epidemiology
 - More common in children and males
- Pathogenesis
 - Postulated to be a response to foreign antigens (infection, drugs)
 - Two forms
 - Acute: pityriasis lichenoides et variolaformis acuta (PLEVA; Mucha-Habermann disease)
 - Chronic: pityriasis lichenoides chronica (PLC; guttate parapsoriasis)
- Contain lesional T-cell infiltrates that may exhibit clonality; may explain occasional association with

other lymphoproliferative disorders such as CTCL, Hodgkin's disease, and other lymphomas

- PLEVA: predominance of CD8 + T cells
- PLC: predominance of CD4 + T cells



FIGURE 8-5 Pityriasis lichenoides. (Reprinted with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003, p. 459.)

- Clinical features
 - PLEVA
 - Individual lesions develop crusts/ulcers/pustules/vesicles → heal to varioliform scars
 - Lesions are asymptomatic and usually resolve within weeks
 - Rarely associated with systemic symptoms: fever, malaise, generalized lymphadenopathy, arthritis, or bacteremia
 - PLC
 - Red/brown scaly papules → heal to hypopigmented macules
 - Lesions are more indolent and regress over weeks to months
 - Duration of disease
 - Diffuse < central < peripheral
- Pathology
 - Superficial perivascular interface dermatitis
 - Focal parakeratosis
 - Epidermal damage: edema to necrosis
 - Erythrocyte extravasation with occasional lymphocytic vasculitis
 - Features are more blunted in chronic lesions
 - Lymphoid atypia is not a standard feature of PL; if present, consider lymphomatoid papulosis
- Treatment
 - Discontinue suspected responsible agent
 - First line: topical corticosteroids, topical coal tar preparations, tetracycline, erythromycin (for children), phototherapy
 - Antibiotics are for anti-inflammatory rather than antibiotic effects
 - Low dose weekly methotrexate for fulminant cases
 - Cases with systemic symptoms – give systemic corticosteroids

Pityriasis Rosea (Pityriasis Rosea Gilbert) (Fig. 8-6)

- Epidemiology
 - Healthy adolescents and young adults
 - No racial predilection
 - Female > male
 - May peak in spring/fall
- Pathogenesis: may have viral etiology as suggested by occasional prodromal symptoms, clustering of cases, and complete absence of recurrent episodes; historically HHV-6 and HHV-7 were considered to be associated but not proven
- Clinical features
 - Herald patch: solitary lesion on trunk that precedes the remainder of the eruption by hours/days; pink/salmon patch/plaque with central fine scale and marginal trailing collerette of scale with free edge pointing inwards
 - Few have mild prodromal symptoms



FIGURE 8-6 Pityriasis rosea. (Courtesy of Dr. Toni Smith.)



FIGURE 8-7 Lichen planus. (Courtesy of Dr. Asra Ali.)

- Blossoming of lesions on trunk/proximal extremities: numerous, smaller, thinner than herald patch; usual round/oval; long axis follows the Langer's lines of cleavage → posterior trunk = "fir tree" or "Christmas tree" pattern
- Face/palms/soles = usually spared
- Persists 6–8 weeks with spontaneous resolution; if lesions last > 5 months → may possibly be PLC instead
- Variant: inverse PR (occurs in axillae/inguinal areas, more common in younger children and darker skin); urticarial, vesicular, purpuric, pustular
- Pathology
 - Non-specific: small mounds of parakeratosis, spongiosis, and mild lymphohistiocytic perivascular and interstitial papillary dermal infiltrate; mild erythrocyte extravasation
 - Most patients do not have biopsies as clinical picture may be classic and histology is non-specific
- Treatment
 - Education/reassurance
 - Counter-irritant antipruritic lotions/low-medium topical corticosteroids
 - Erythromycin, UVB light

Lichen Planus (Fig. 8-7)

- Epidemiology
 - No racial/gender predisposition
- Pathogenesis
 - T-cell mediated autoimmune damage to basal keratinocytes that express altered self-antigen on their surface secondary to exposure to exogenous agents

- Exogenous agents
 - Hepatitis C virus (associated with HLA-DR6)
 - Transfusion-transmitted virus (TTV)
 - HHV-6
 - HBV vaccine
 - Oral contact allergens (metallic dental restorations/reconstructions [amalgum/mercury, copper, gold])
 - Drugs: captopril, enalapril, labetalol, methyl-dopa, propranolol, chloroquine, hydroxychloroquine, quinacrine, chlorothiazide, HCTZ, gold salts, penicillamine, quinidine
 - Paraneoplastic process
- Clinical features
 - Peak onset in 5th–6th decade
 - Pruritic violaceous papules – small, polygonal, flat-topped, occasionally umbilicated; shiny/transparent surface
 - Fine white lines = Wickham's striae
 - Distribution: flexor surface of wrists/forearms, dorsal surface of hands, anterior lower legs, neck, and presacral areas
 - Mucosal involvement in ~ 75% of patients with cutaneous LP
- Variants
 - Actinic LP/LP tropicus/lichenoid melanoderma-titis: occurs in spring/summer on sun-exposed skin with red/brown plaques
 - Acute LP/exanthematous LP/eruptive LP: widely distributed with rapid dissemination
 - Annular LP: papules spread peripherally and central area resolves; annular edge is raised and purple to white in color. Usually on axilla or penis

- *Atrophic LP*: papules coalesce to form larger plaques that become centrally depressed/atrophic with residual hyperpigmentation; secondary to thinning epidermis and not due to degeneration of elastic fibers
- *Bullous LP*: bullous or vesiculobullous lesions develop within pre-existing LP
- *LP pemphigoides*: bullous or vesiculobullous lesions develop on previously uninvolved skin; have circulating IgG autoantibodies
- *Hypertrophic LP/LP verrucosus*: extremely pruritic, thick hyperkeratotic plaques on shins/dorsal foot; may have fine adherent scale; usually symmetric and chronic; may lead to squamous cell carcinoma
- *Inverse LP*: violaceous papules/plaques in intertriginous zones
- *LP pigmentosus*: occurs in patients with skin types III–IV as brown/gray macules in sun-exposed areas of face/neck; reticulated pigmentation; can have linear distribution following Blaschko's lines
- *Lichen planopilaris/follicular LP/LP acuminatus*: multiple hyperkeratotic plugs with narrow violaceous rim primarily on scalp resulting in scarring and alopecia. Women > men
- *Linear LP*: spontaneously occur within the lines of Blaschko
- *LP-lupus erythematosus overlap syndrome*: prefers acral sites
- *Nail LP*: lateral thinning, longitudinal ridging and fissuring; can lead to dorsal pterygium formation
- *Oral LP*: reticular pattern is the most common = whitish linear lines in a lace-like pattern or rings with short radiating spines; buccal mucosa > gingival; check for esophageal and genital involvement
- *Vulvovaginal LP*: erosions; can evolve into malignancy
- Pathology
 - Hyperkeratosis without parakeratosis
 - Focal increases in granular cell layer
 - Irregular acanthosis with a "saw-tooth" appearance
 - Liquefactive degeneration of the basal cell layer
 - Band-like lymphocytic infiltrate at dermal-epidermal junction
 - Small separations between dermis and epidermis (Max-Joseph spaces)
 - Oral LP: parakeratosis rather than hyperkeratosis
- Treatment
 - Spontaneous remission of cutaneous LP in 2/3 of patients after 1 year; whereas oral LP lasts ~ 5 years (erosive form rarely resolves)
 - Topical corticosteroids

- Topical calcineurin inhibitors
- Intralesional corticosteroids – especially for hypertrophic LP
- Miscellaneous: griseofulvin, metronidazole, cyclosporine, mycophenolate mofetil
- Phototherapy
- Systemic steroids – first line for severe acute cutaneous LP

Lichenoid Keratosis (Lichen Planus-Like Keratosis)

- Epidemiology
 - 35–65 years old; women > men
 - mostly Caucasians
- Pathogenesis
 - Thought to represent inflammation of a benign lentigo (benign lichenoid keratosis, BLK), actinic keratosis (lichenoid actinic keratosis), or SK (irritated SK)
 - Suggested that lichenoid infiltrate of lymphocytes is secondary to a stimulus from Langerhans cells after their processing of an unidentified epidermal antigen (similar to mechanism for lichen planus)
- Clinical features
 - Solitary pink to red/brown, often scaly, papules ranging 0.3–1.5cm in diameter; most closely resembles a BCC (most frequent reason for biopsy)
 - Usually asymptomatic but can have slight pruritus/stinging
 - Distribution: forearm and upper chest > shins (women) > chronically sun-exposed areas
- Pathology
 - Lichenoid infiltrate of lymphocytes with scattered histiocytes
 - Interface dermatitis: basal vacuolar alteration, melanin incontinence, colloid bodies
 - May see parakeratosis (unlike lichen planus)
 - Sometimes frank separation of epidermis from dermal infiltrate → subepidermal blister/cleft
- Treatment: none necessary; can destroy any remaining lesions by any method

Lichen Nitidus

- Epidemiology: rare disease – poor data
- Pathogenesis: limited study; no causative agents discovered
- Clinical features
 - Tiny discrete skin-colored uniform pinhead-sized papules with occasional central depression; usually flat with shiny surface
 - Distribution: flexor surface of upper extremities, genitalia, chest, abdomen, dorsal hands
 - Oral lesions: minute, flat, gray/white papules on soft mucosa or white plaques on tongue/hard palate
 - Nails (10%): pitting, rippling, longitudinal ridging, terminal splitting, increased

longitudinal linear striations, occasional periungual papules

- Exhibits Koebner phenomenon
- Pathology
 - Well-circumscribed infiltrate of lymphocytes, epithelioid cells, and occasional Langhans giant cells that are “clutched” by surrounding hyperplastic rete ridges in a “ball and claw” configuration
 - Epidermis is atrophic +/- parakeratotic “cap” centrally
 - Absence/thinning of granular layer
 - Liquifactive degeneration of basal layer
- Treatment
 - Most patients have spontaneous clearing within one to several years
 - Primarily symptomatic (topical steroids, oral antihistamines)
 - Topical calcineurin inhibitors
 - Narrowband UVB or PUVA

Lichen Striatus (Linear Lichenoid Dermatoses/ Blaschko Linear Acquired Inflammatory Skin Eruptions [BLAISE]) (Fig. 8-8)

- Epidemiology: female > male; primarily children (4mo–15yrs)
- Pathogenesis: theory: during fetal development, aberrant clones of epidermal cells produced by somatic mutation migrate out along lines of Blaschko → exposure to infectious agent triggers intolerance by inducing novel membrane antigen
- Clinical features
 - Typically asymptomatic



FIGURE 8-8 Lichen striatus. (Courtesy of Dr. Jason Miller.)

- Continuous/interrupted band of discrete/clustered pink/skin-colored/tan papules that are flat-topped/smooth/scaly, 2–4mm in size
- Typically a single unilateral streak on an extremity
- Appears suddenly → develops over days/weeks → spontaneous resolution after a year or more with post-inflammatory hypopigmentation
- Pathology
 - Depends on age of lesion
 - Lichenoid tissue reaction with parakeratosis, dyskeratosis, and focal/diffuse lysis of basal layer
 - Langerhans cells are decreased (early) or increased (late)
- Treatment: not needed except for significant pruritus (topical corticosteroids)

Erythema Dyschromium Perstans (Ashy Dermatoses/Dermatitis)

- Epidemiology
 - Darkly pigmented Latin Americans > Asians > Whites
 - Favors skin types III + IV
 - No gender predisposition
 - Onset: 1st–3rd decade
- Pathogenesis: sporadic case reports of temporal associations with ingestion of ammonium nitrate, whipworm infestation, and HIV seroconversions
- Clinical features
 - Gray/brown/blue macules/patches
 - Uncommon erythematous peripheral margin measuring 1–2mm in width
 - Lesion is usual oval in shape with long axes following skin cleavage lines (similar pattern to pityriasis rosea)
 - Distribution: neck, trunk, proximal arms; usually symmetric; sparing of palms, soles, scalp, nails, and mucous membranes
 - Spontaneous clearing can occur in children but usually persists for years in adults
- Pathology
 - Border of active lesions: vacuolization of basal layer, occasional colloid bodies, lichenoid infiltrate of varying degrees
 - Immunofluorescence: IgM, IgG, fibrinogen, C3 staining colloid bodies (like in LP)
 - Inactive ashy-colored lesions: pigment incontinence, variable epidermal change, including atrophy and effacement of epidermal ridges
- Treatment
 - Usually not effective
 - Sun protection
 - Topical corticosteroids/retinoids
 - Vitamin C, chemical peels, oral antibiotics, vitamin A, dapsone, antimalarials, griseofulvin, oral corticosteroids

Transient Acantholytic Dermatitis (Grover's Disease)

- Epidemiology
 - Caucasian men > 40 years old
 - Peak in winter months
- Pathogenesis
 - Exact etiology unknown; may be secondary to acute/chronic radiation (UV or ionizing), excessive sweating (on the back of a febrile bedridden patient), heat, and xerosis
 - Predisposition with asteatotic, atopic, and allergic contact dermatitis
- Clinical features
 - Discrete round papules/papulovesicles: skin-colored or erythematous, crusted, extremely pruritic
 - Distribution: upper/mid trunk > lower trunk/proximal extremities
 - Can be acute, chronic, or relapsing
 - Exacerbations with heat, friction, sweating, and sunlight exposure
- Pathology
 - Focal acantholysis and dyskeratosis in association with intraepidermal clefting and vesicle formation
 - Four histological variants (more than one pattern can be seen in the same biopsy specimen)
 - Darier disease-like
 - ▲ Suprabasal cleft formation
 - ▲ Most pronounced dyskeratotic changes (corps ronds and grains)
 - Hailey-Hailey disease-like
 - ▲ Clefting in stratum spinosum
 - Pemphigus vulgaris or foliaceus-like
 - ▲ PV-like: subbasal cleft formation
 - ▲ PF-like: clefting in superficial epidermis
 - Spongiotic with acantholysis
 - Direct immunofluorescence is negative
- Treatment
 - Avoid exacerbators – sunlight, exercise, occlusive fabrics, heat
 - First line: topical corticosteroids
 - Topical calcipotriol and topical calcineurin inhibitors
 - More aggressive: phototherapy, oral corticosteroids, PUVA, UVA1, trichloroacetic acid peel

- Pathogenesis
 - EAC is a poly-etiological “allergic” reaction
 - Incidentally, there is a relationship between EAC and chronic infectious diseases, arthropod bites and intake of drugs or internal neoplasms
- Clinical features
 - Trunk, extremities most commonly affected
 - Urticarial erythematous annular or polycyclic lesions
 - Centrifugal spread, regression in the center
 - Trailing scale is present on the inner aspect of the advancing edge
 - Middle-aged adults
 - Healing in weeks up to years
- Pathology: intense, superficial, and deep lymphocytic or lymphohistiocytic perivascular infiltrate in a coat-sleeve fashion in the middle and lower dermis
- Treatment: self-limited; treat underlying disorder; topical, systemic or injection steroid therapy

Erythema Gyrratum Repens (EGR)

- Epidemiology: associated with malignancy in as many as 80% of patients; often precedes the detection of malignancy
- Pathogenesis
 - Associated malignancies: lung (most common), breast, urinary bladder, uterus and/or cervix, gastrointestinal tract (stomach), and prostate
 - Associated with some nonneoplastic conditions: pulmonary tuberculosis, lupus erythematosus, CREST (calcinosis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia) syndrome
- Clinical features
 - Clinical findings: wood-grain appearance; concentric mildly scaling bands of patches or plaques of erythema; rapid migration (up to 1 cm/day); intense pruritus
 - Course of rash closely mirrors the course of the underlying illness
 - Spongiosis, focal parakeratosis, and a superficial perivascular lymphohistiocytic infiltrate, with eosinophils and melanophages; exocytosis of neutrophils and eosinophils
- Treatment: steroids for pruritus; symptoms disappear with resolution of underlying disease

URTICARIA

- Epidemiology
 - Any age
 - More common in women: chronic urticaria, dermatographism, cold urticaria
 - More common in men: pressure urticaria

FIGURATE ERYTHEMAS

Erythema Annulare Centrifugum (Erythema Figuratum)

- Epidemiology: unknown

- Pathogenesis
 - High affinity IgE receptors are crosslinked, which initiates a chain of calcium/energy-dependent steps leading to fusion of storage granules and externalization of contents (degranulation)
 - Degranulation can also be stimulated by anti-IgE and anti-IgE receptor antibodies, opiates, C5a anaphylatoxin, stem cell factor, neuropeptides (substance P)
 - Mast cell granules contain histamine, cytokines (TNF-alpha, interleukins [3, 4, 5, 6, 8, 13]), GM-CSF, proinflammatory eicosanoids (prostaglandin [PGD2], leukotrienes [LTC4, D4, E4])
- Clinical features
 - Multiple pruritic wheals of different sizes erupt anywhere on the body and then fade within 2–24 hours without bruising; often appears in evening or upon waking; most intense at night
 - In severe cases: can be associated with fatigue, lassitude, sweats, chills, indigestion, arthralgias
 - *Acute urticaria*
 - ▲ Duration < 6 weeks
 - ▲ Triggers: 50% idiopathic, 40% viral URI, 9% drugs, 1% food
 - ▲ Common in children with atopic dermatitis
 - *Chronic urticaria*
 - ▲ Duration > 6 weeks and continuous (occurs at least 2x/wk when off of treatment)
 - ▲ Associations with HLA-DR4 and HLA-DQ8, *H. pylori* gastritis, and intestinal strongyloidiasis
 - ▲ Triggers: 60% ordinary (autoimmune, pseudoallergic, infection-related, idiopathic), 35% physical, 5% vasculitic
 - *Episodic urticaria*
 - ▲ Duration > 6 weeks but not continuous
 - *Physical urticaria*: induced by exogenous physical stimulus; lesions occur within minutes of provocation and generally resolve < 2 hours and are localized to the stimulated area
 - ▲ Triggered by mechanical stress
 - △ Dermatographism (factitious urticaria)
 - △ Delayed pressure urticaria (DPU)
 - △ Vibratory angioedema (see AE section)
 - ▲ Triggered by temperature changes
 - △ Heat/stress = cholinergic urticaria
 - △ Adrenergic urticaria
 - △ Localized heat contact urticaria
 - △ Primary/secondary cold contact urticaria
 - △ Reflex cold urticaria
 - △ Familial cold urticaria
- ▲ Triggered by other exposures
 - △ Primary/secondary solar urticaria
 - △ Aquagenic urticaria
 - *Contact urticaria*
 - ▲ Immunologic (allergic reaction with specific IgE): sensitized to environmental allergens (grass, animals, foods)
 - ▲ Non-immunologic (IgE-independent): secondary to direct effects of urticants on blood vessels (cinnamic aldehyde in cosmetics, nettle stings)
- Pathology: perivascular infiltrate of lymphocytes and eosinophils with some neutrophils with extension of eosinophils into the dermis, arrayed between collagen bundles
- Treatment
 - Antipruritic lotions and avoidance of triggers
 - First line: antihistamines (first H1 antihistamine, then add H2 antagonist if necessary)
 - Second line: systemic corticosteroids (for emergencies; avoid in chronic urticaria), epinephrine (for severe throat angioedema/anaphylaxis only), doxepin combos
 - Third line: immunotherapy (for severe refractory autoimmune urticaria only): IVIG, cyclosporine, plasmapheresis

Angioedema (AE)

- Epidemiology: hereditary form is AD
- Pathogenesis
 - Hereditary AE: mutation in structural gene for C1 inhibitor leading to
 - Reduced quantity (type 1) secondary to trans inhibition of the normal allele or increased catabolism of C1 INH
 - Reduced function (type 2)
 - Acquired AE: secondary to formation of inhibitory autoantibodies against C1 INH or persistent low-level activation of C1q by anti-idiotypic antibodies
- Clinical features
 - Can merge with wheals, especially at eyelids
 - Can be a feature of anaphylaxis if the throat is involved
 - AE without wheals is a separate clinical entity as this occurs in C1 INH deficiency, ACEi or NSAID reactions, and are managed differently
 - Hereditary AE: low C4
 - Acquired AE: low C4 and low serum C1q
 - Vibratory AE: hereditary (AD) or acquired; vibratory stimulus (jogging, motorcycles) lead to localized swelling and erythema in minutes
 - Food/exercise-induced anaphylaxis: occurs within minutes of exercise after prior ingestion of specific foods or within 4 hours of a heavy meal

- Treatment
 - See urticaria treatment section above
 - For C1 esterase inhibitor deficiency
 - Emergency: give C1 inhibitor concentrate or FFP (life-saving) [acquired deficiency patients need more than hereditary]
 - Antihistamines, corticosteroids, and epinephrine do not work
 - Treatment of choice: anabolic steroids (stanozolol or danazol)

Urticarial Vasculitis

- Epidemiology: Middle-aged women
- Clinical features
 - Actually considered an urticarial dermatosis and not urticaria
 - Lesions last > 24 hours (unlike urticaria) although clinically appears like urticaria
 - Lesions are pruritic and/or painful (burning sensation)
 - Often occurs at pressure points and may resolve with residual pupura
 - 40% develop angioedema; 50% develop arthralgia (transient/migratory)
 - Course is unpredictable and usually more severe in hypocomplementemic patients
 - Acute hemorrhagic edema of childhood: urticarial vasculitis with prominent cutaneous hemorrhage in young children
- Pathology
 - Evidence of leukocytoclastic vasculitis, fibrinoid deposits in/around blood vessels, extravasation of red cells, endothelial cell swelling, perivenular cellular infiltrate rich in neutrophils
 - Need to biopsy a lesion that is < 24 hours old for accuracy
- Treatment
 - No universally effective therapy (no randomized trials)
 - Antihistamines are usually insufficient except in mild cases
 - 50% improve with NSAIDs
 - Isolated positive reports with colchicine, dapsone, hydroxychloroquine

Other Figurate Erythemas (Covered in Separate Chapters)

- Bullous pemphigoid
- Erythema annulare centrifugum
- Erythema multiforme
- Glucagonoma syndrome
- Granuloma annulare
- Lupus erythematosus, subacute cutaneous
- Lyme disease
- Pityriasis rubra pilaris

- Psoriasis, plaque
- Tinea corporis

Id Reaction (Autoeczematization)

- Epidemiology: exact prevalence unknown
- Pathogenesis
 - Exact cause of the id reaction is unknown
 - Abnormal immune recognition of autologous skin antigens
 - Increased stimulation of normal T cells by altered skin constituents
 - Lowering of the irritation threshold
 - Dissemination of infectious antigen with a secondary response
 - Hematogenous dissemination of cytokines from a primary site
- Clinical features
 - Symmetric, pruritic, erythematous, maculopapular, or papulovesicular eruption at a site distant from the primary infection or dermatitis
 - Begins 1 to 2 weeks after primary infection or dermatitis
- Pathology
 - Superficial perivascular lymphohistiocytic infiltrate with a spongiotic epidermis and vesiculation
 - Infectious agents not found in the specimens
- Treatment
 - Systemic or topical corticosteroids
 - Wet compresses
 - Systemic or topical antihistamines

ACROKERATOSIS VERRUCIFORMIS OF HOPF

- Epidemiology: AD
- Clinical features: flat wart-like papules on the dorsal aspects of the extremities; debatable if truly a separate disease vs part of Darier's disease

HAILEY-HAILEY DISEASE

- Epidemiology: AD
- Pathogenesis
 - Mutations in the gene ATP2C1 that encodes the Golgi-associated Ca^{2+} ATPase
 - Golgi Ca^{2+} depletion may impair complete processing of junctional proteins, resulting in a loss of cellular adhesion in the stratum spinosum (acantholysis)
- Clinical features
 - Initial symptoms and lesions usually develop during the second or third decade
 - Sites of predilection include intertriginous areas, lateral neck
 - Initial lesion is a flaccid vesicle on erythematous or normal skin, which easily ruptures

- Blisters give rise to macerated or crusted erosions, which spread peripherally
- Healing occurs with scarring and dyspigmentation
- Pruritus and malodor are common
- Friction, heat and sweating worsen disease
- Bacterial colonization and secondary bacterial, fungal and viral infections can complicate the disease (i.e., Kaposi's varicelliform eruption)
- Rarely malignant transformation
- Pathology: "delapidated brick wall" appearance of epidermis due to acantholysis
- Treatment
 - Lightweight clothing
 - Topical and systemic antimicrobials as needed
 - Topical corticosteroids
 - Wide excision with grafting
 - Dermabrasion
 - PDT or laser resurfacing

Granuloma Faciale (Fig. 8-9)

- Epidemiology: idiopathic; predominantly in middle-aged white men
- Pathogenesis: unknown
- Clinical features
 - Solitary, asymptomatic smooth red-brown to violaceous plaque on the face
 - Predominantly on the face
 - Chronic and only occasionally spontaneously resolves
 - Not associated with systemic disease
- Pathology: normal epidermis, Grenz zone and a dense, nodular and diffuse infiltrate of



FIGURE 8-9 Granuloma faciale. (Reprinted with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003, p. 967.)

lymphocytes, neutrophils, plasma cells and eosinophils in the dermis

- Treatment
 - Often resistant to therapy
 - IL corticosteroids
 - Oral dapsone or clofazimine
 - PUVA

Sweet's Syndrome (Acute Febrile Neutrophilic Dermatositis) (Fig. 8-10)

- Epidemiology
 - Worldwide distribution
 - Female predominance 4:1
 - Average age of onset 30–60 years
 - Up to 20% have internal malignancies (no female predominance)
 - Drug induced cases occurs more often in women
- Pathogenesis: unknown
- Clinical features
 - Initial cutaneous lesions are tender, non-pruritic, erythematous plaques or papules, which may coalesce
 - Vesiculobullous variant most frequently associated with myelogenous leukemia and can break down with ulceration



FIGURE 8-10 Acute febrile dermatosis (Sweet's syndrome). (Reprinted with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003, p. 951.)

- Favors the head, neck and upper extremities, but tends to be more widespread when associated with malignancy
- An upper respiratory tract infection or flu-like illness frequently precedes the development of the syndrome
- Fever is common
- Extracutaneous involvement common, including ocular involvement, arthralgias, myalgias, arthritis, neutrophilic pulmonary alveolitis, multifocal sterile osteomyelitis
- Associated diseases include the following
 - Streptococcal infection
 - GI yersiniosis
 - Hematologic malignancy (especially AML)
 - Solid tumors—carcinoma of the GU tract, breast and colon
 - Inflammatory bowel disease
 - Drugs (GM-CSF, furosemide, hydralazine, minocycline, Bactrim and all-trans-retinoic acid)
 - Autoimmune disease: SLE, Behcet's autoimmune thyroid disease, dermatomyositis, sarcoid
- Diagnostic criteria: (requires 2 major and 2 minor)
 - Major criteria
 - Abrupt onset of typical cutaneous lesions
 - Histopathology consistent with Sweet's syndrome
 - Minor criteria
 - Preceded by one of the associated infections or vaccinations; accompanied by one of the associated malignancies or inflammatory disorders; associated with drug exposure or pregnancy
 - Presence of fever and constitutional signs and symptoms
 - Leukocytosis
 - Excellent response to corticosteroids
- Pathology
 - Papillary dermal edema
 - Dense diffuse dermal nodular and perivascular neutrophilic infiltrate without vasculitis
- Treatment
 - Cutaneous lesions may involute spontaneously
 - Recurrences occur in 30% (with or without treatment)
 - Treatment of underlying condition
 - Oral prednisone (0.5–1 mg/kg/day) for 4–6 weeks

Pyoderma Gangrenosum (Fig. 8-11)

- Epidemiology
 - Most commonly women between 20–50 years old
 - 50% have underlying systemic disease (Inflammatory bowel disease, arthritis, and myeloproliferative disorders)



FIGURE 8-11 Pyoderma gangrenosum. (Courtesy of Dr. Jason Miller.)

- Pathogenesis
 - idiopathic in 25–50%
 - immunologic abnormality (autoimmune)
 - 15% have monoclonal gammopathy (usually IgA)
 - PAPA syndrome (pyogenic sterile arthritis, PG, and acne): mutations in CD2 binding protein 1, which is thought to lead to an abnormal inflammatory response
- Clinical features
 - Painful cutaneous lesions that occur on lower extremities (pretibial) but can occur anywhere
 - Start as a tender papulopustule/bulla/nodule with surrounding erythematous/violaceous base
 - All lesions undergo necrosis leading to a central shallow/deep ulcer with a purulent base and irregular, undermined/overhanging gunmetal-colored border that extends centrifugally
 - Re-epithelialization occurs from the margins and heals with atrophic cribriform pigmented scars
 - Lesion number varies from one to over a dozen and can coalesce
 - Classically described as rapidly expanding but can be more indolent
 - Variants
 - Vesiculobullous form (atypical or bullous PG)
 - ▲ Associated with AML, myelodysplasia, and myeloproliferative disorders (CML)
 - ▲ Favors face and upper extremities (dorsal hands)
 - Pustular PG
 - ▲ Associated with IBD
 - ▲ Multiple small sterile pustules that regress without scarring

- Superficial granulomatous PG
 - ▲ Associated with trauma, i.e., surgery
 - ▲ Localized superficial vegetative/ulcerative lesion; favors the trunk
- Pyostomatitis vegetans: associated with IBD; chronic vegetative sterile pyoderma of labial/buccal mucosa
- Children: favors head, genital, and perianal areas
- Pathology
 - Non-specific, especially if partially treated or minimally inflamed
 - Early lesions: neutrophilic vascular reaction that may be folliculocentric
 - Active lesions: neutrophilic infiltrates with leukocytoclasia
 - Fully developed ulcers: necrosis with surrounding mononuclear cell infiltrates and fibrosing inflammation at the edge of the ulcer
- Treatment
 - First line: local +/- systemic corticosteroids +/- adjunctive systemic therapies
 - 2nd line: cyclosporine, tacrolimus, thalidomide
 - For concomitant Crohn's disease: infliximab
 - Total colectomy for ulcerative colitis is not a guaranteed cure for associated PG



FIGURE 8-12 Granuloma annulare. (Reprinted with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003, p. 981.)

GRANULOMATOUS PROCESSES

Granuloma Annulare (Pseudorheumatoid Nodule) (Fig. 8-12)

- Epidemiology
 - Two-thirds are < 30 years of age
 - Female: male: 2:1
 - Pathogenesis
 - Etiology unknown but postulated to be a delayed-type hypersensitivity reaction to an unknown antigen (possibly a TH1-mediated inflammatory reaction)
 - Thought to be primarily a disorder of elastic tissue injury
 - Rare familial cases reported: associated with HLA-Bw35
 - Clinical features
 - Self-limited benign disease
 - Annular plaques that favor the extremities: hands/arms > legs/feet > trunk
 - Plaques can be skin-colored, violaceous, or pink and are composed of individual small papules that can be umbilicated
 - Variants
 - Generalized GA: symmetric distribution on trunk and extremities; later age of onset; poorer response to therapy; increased
- prevalence of HLA-Bw35 allele; 45% have lipid abnormalities
- Perforating GA: small papules with central umbilications/crusts/ulcerations on dorsal hands/fingers; exhibits transepidermal elimination of degenerating collagen histologically
 - Deep dermal/subcutaneous GA: large, painless, skin-colored nodules = "pseudorheumatoid nodules"; more common in children 5-6 yo
 - Patch GA: patches of erythema on extremities/trunk or symmetrical lesions on dorsal feet; can lack annular configuration
 - Paraneoplastic GA: associated with solid tumors, Hodgkin disease, non-Hodgkin lymphoma, and granulomatous mycosis fungoides
- Classic GA and perforating GA can occur in herpes zoster scars
 - Pathology
 - Focal degeneration of collagen and elastic fibers, mucin deposition, and a perivascular/interstitial lymphocytic infiltrate in the upper/mid dermis
 - Histiocyte patterns
 - Infiltrative/interstitial: scattered histiocytes between collagen fibers with mucin deposition between collagen bundles (highlighted with Alcian blue and colloidal iron stains)
 - Palisading granulomas: with central connective tissue degeneration surrounded by histiocytes and lymphocytes; mucin is abundant in the center of the granuloma (more common in deep GA)
 - Epithelioid histiocytic nodules (like sarcoidosis)

- Vascular changes: variable; can have fibrin, C3, and IgM deposition in vessel walls with occlusion; can be predictive of associated systemic disease
- Treatment
 - Localized/asymptomatic disease: reassurance/observation
 - First line: high-potency topical corticosteroids +/- occlusion, intralesional corticosteroid injections
 - Cryosurgery, PUVA/UVA1, CO2 laser, dapsone
 - Spontaneous resolution in 50% but recurrence in 40% (occurs at original sites but clears more rapidly)

Actinic Granuloma (Annular Elastolytic Giant Cell Granulomas)

- Clinical presentation
 - Annular/serpiginous areas with raised erythematous borders
 - Located on heat/sun-damaged skin
 - Presents with 1–10 plaques
- Pathology: may lack the classic palisaded arrangement observed in GA; elastosis is abundant in the mid-dermis outside the granuloma; elastic tissue is absent from the center

Chondrodermatitis Nodularis Helices

- Epidemiology: occurs in adults > 40 yo
- Pathogenesis
 - Predisposing factors: actinic damage, cold exposure, trauma, local ischemia, radiotherapy
 - Helical lesions: may begin with perichondritis/folliculitis
 - Antihelical lesions: may begin with pressure-induced ischemia, involving the cartilage secondarily
- Clinical features
 - Skin-colored to erythematous dome-shaped nodules with central crusts or keratin-filled craters
 - Most occur on upper helical rim or the mid-lower antihelical rim; sites often correspond to outermost portions of pinna
 - Often exquisitely tender to palpation
 - Women: commonly on antihelix
 - Men: commonly on helix
- Pathology
 - Well-circumscribed area of acanthosis, parakeratosis, and hypergranulosis
 - Central crater with epidermal disruption +/- keratotic plug/dermal debris
 - Lymphohistiocytic infiltrate extends into thickened perichondrium
- Treatment
 - Relieve/eliminate pressure (special “donut hole” pillows)
 - Topical corticosteroids/antibiotics

- Surgery: cryosurgery, electrodesiccation and curettage, full-thickness excision, CO₂ laser ablation

Sarcoidosis (Fig. 8-13)

- Epidemiology
 - Bimodal age distribution: peaks at 25–35 years and 45–65 years
 - In the United States: higher incidence in African-Americans, who have more acute and severe disease (commonly 40 yo African-American female)
 - New-onset most common in winter/spring
- Pathogenesis
 - Upregulation of CD4+ T-helper cells of Th1 subtype after antigen presentation → epithelioid granulomas
 - Etiology unknown: may be autoimmune or infectious
 - Genetic susceptibility: HLA-1, HLA-B8, HLA-DR3 alleles; ACE gene polymorphisms
- Clinical features
 - Papules/plaques – red/brown, yellow/brown, erythematous, or violaceous (lupus pernio)
 - Favor the face, lips, neck, and upper trunk/extremities
 - Usually fairly symmetric without scale
 - Commonly develop within pre-existing scars or sites of prior trauma
 - Upon diascopy, pressure induces blanching and lesions appear to have “apple jelly” color
 - Can have prominent telangiectasias = angiolupoid sarcoidosis

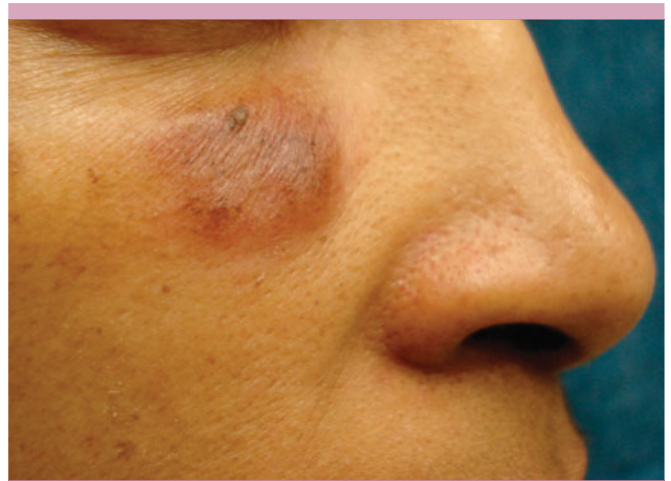


FIGURE 8-13 Sarcoidosis. (Courtesy of Dr. Asra Ali.)

- Variants
 - Darier-Roussy sarcoidosis: painless, firm, mobile nodules without epidermal involvement
 - Lupus pernio: papulonodules/plaques in areas affected by cold (nose, ears, cheeks); often with beaded appearance on nasal rim; 75% have lung involvement; 50% have upper respiratory tract involvement
- Löfgren's syndrome: erythema nodosum with hilar adenopathy, fever, migrating polyarthritis, and acute iritis
- Nail changes: clubbing, subungual hyperkeratosis, onycholysis
- Heerfordt's syndrome: parotid gland enlargement, uveitis, fever, and cranial nerve palsies (usually of the facial nerve)
- Pathology
 - Superficial and deep dermal epithelioid cell granulomas without any lymphocytes or plasma cells (naked tubercles)
 - No central caseation
 - Multinucleated giant cells are usually Langhans type, with nuclei arranged in a peripheral arc
 - Asteroid bodies: eosinophilic stellate inclusions, likely engulfed collagen
 - Schaumann bodies: rounded laminated basophilic inclusions, likely degenerating lysosomes
 - Kveim test: intradermal injection of tissue from spleen or lymph node of a patient with sarcoidosis; biopsy sample is obtained from the area 4–6 weeks after injection
- Treatment
 - Corticosteroids (topical, intralesional, or systemic)
 - Hydroxychloroquine, chloroquine
 - Methotrexate, thalidomide, isotretinoin, minocycline, allopurinol

Foreign-Body Granulomas

- Epidemiology: occurs in both children and adults and the general health of the patient is unaffected
- Pathogenesis: foreign body granulomas occur because foreign material remains undigested
- Clinical features
 - Located in areas of trauma and surgery
 - Small, firm nodules, often surrounded by inflammation
 - Red, red-brown, or color of normal skin
 - Ulcerations and fistula
- Pathology
 - Foreign bodies (suture material, keratin, hair, traumatic foreign material)
 - Chronic inflammation with giant multinuclear histiocytes and granulocytes; some foreign

bodies (silica, wood, suture material, glass) are birefringent (identify with polarized light)

- Treatment: surgical removal of the foreign body

CUTANEOUS DISORDERS OF INFILTRATION

Scleromyxedema (Generalized and Sclerodermoid Lichen Myxedematosus)

Chronic idiopathic disorder characterized by numerous firm papules and areas of induration that are due to dermal mucin deposition in association with an increase of dermal collagen

- Epidemiology: affects middle-aged adults of both sexes equally
- Pathogenesis: unknown; significance of monoclonal gammopathy is uncertain
- Clinical features
 - Numerous 2–3 mm firm, waxy closely spaced papules develop in a widespread symmetrical distribution pattern
 - Most common sites are hands, forearms, neck
 - Almost always associated with monoclonal gammopathy—IgG with γ light chains
 - Less than 10% progress to multiple myeloma
 - Can have internal manifestations: muscular, neurologic, rheumatologic, pulmonary, renal, and cardiovascular
- Pathology
 - Diffuse deposits of mucin in the upper and mid reticular dermis
 - Increase in collagen
 - Marked proliferation of irregularly arranged fibroblasts
- Treatment
 - Monthly courses of melphalan
 - Intralesional and topical corticosteroids
 - PUVA, systemic retinoids, extra corporeal photopheresis, thalidomide, electron beam radiation
 - Autologous stem cell transplant

Localized Variants of Lichen Myxedematosus

- Clinical features
 - Small, firm, waxy papules limited to a few sites (upper and lower limbs and trunk)
 - Skin is the only site of involvement
 - Not associated with sclerosis, paraproteinemia, systemic involvement or thyroid disease
 - Four subtypes
 1. Discrete papular form
 2. Acral persistent papular mucinosis
 3. Cutaneous mucinosis of infancy
 4. Pure nodular form

- Associated with HIV, exposure to toxic oil or L-tryptophan, hepatitis C virus

Colloid Milium

- Clinical features
 - Grouped whitish papules on sun-exposed skin—dorsal hands, face, neck, ears
 - Three forms: nodular, adult onset and juvenile (AD)
- Pathology
 - Nodular fissured masses of amorphous eosinophilic material in the superficial dermis
 - Congo red and crystal violet often stain positive
- Treatment: dermabrasion, cryotherapy, diathermy

Favre-Racouchot Syndrome (Fig. 8-14)

- Clinical features
 - Multiple large open comedones develop on the lateral in inferior aspects of the periorbital area
 - Associated with marked solar elastosis
- Pathology: dilated pilosebaceous openings and cyst-like spaces filled with horny material

Erythema Elevatum Diutinum

- Epidemiology
 - Any age but more common in middle-aged and older adults
 - Male to female ratio is equal
 - No racial predilection
- Pathogenesis
 - Associated infections: β -hemolytic streptococcus, HIV, hepatitis B virus
 - Associated autoimmune or inflammatory conditions: Wegener's granulomatosis, inflammatory bowel disease, relapsing polychondritis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA)



FIGURE 8-14 Favre racouchot. (Courtesy of Dr. Asra Ali.)

- Associated hematologic disorders: plasma cell dyscrasias, myelodysplasia, myeloproliferative disorders, hairy cell leukemia
- Immune complex deposition as a result of chronic antigenic exposure or high circulating antibody levels are thought to be the underlying pathologic mechanism
- Clinical features
 - Red-violet to red-brown papules, plaques and nodules that favor extensor surfaces
 - Arthralgias can develop in underlying joints
 - Chronic course, but majority resolve spontaneously over 5–10 years
- Pathology
 - Neutrophilic infiltrate in the upper and mid dermis with eosinophils
 - Late stage lesions with extracellular cholesterol deposits and fibrosis
- Treatment
 - Dapsone with relapse upon discontinuation
 - NSAIDs, niacinamide, tetracyclines, chloroquine, colchicine, plasmapheresis
 - Intralesional corticosteroids

Scleredema

Symmetrical diffuse induration of the upper part of the body caused by a thickened dermis and depositions of mucin

- Epidemiology
 - Affects all races
 - Associated with diabetes (more commonly in men)
 - Other forms more common in women
- Pathogenesis
 - Diabetes mellitus
 - Irreversible glycosylation of collagen and resistance to degradation by collagenase may lead to an accumulation of collagen
 - Excess stimulation by insulin, microvascular damage and hypoxia may increase the synthesis of collagen and mucin
 - Streptococcal hypersensitivity, injury to lymphatics and paraproteinemia may play a role
- Clinical features
 - First type—affects primarily middle-aged women and children and is preceded by fever, malaise, and upper or lower respiratory tract infection (usually Streptococcal); cervicofacial skin hardens and extends to trunk and proximal upper limbs; can get tongue and pharyngeal involvement; resolves in a few months
 - Second type—same as first but with more subtle onset, without a preceding illness and persists for years; associated with monoclonal gammopathy

- Third type—affects obese, middle-aged men with insulin dependent DM; subtle onset with persistent involvement; primarily involves posterior neck and back
- Systemic manifestations include serositis, dysarthria, dysphagia, myositis, parotitis, ocular and cardiac abnormalities
- Associated with hyperparathyroidism, RA, Sjogren's syndrome, malignant insulinoma, malignant melanoma, gallbladder carcinoma, HIV
- Pathology
 - Thickening of the reticular dermis with large collagen bundles separated by clear spaces filled with mucin
 - No increase in the number of fibroblasts
 - Mucin accumulates in the skeletal muscle and heart
- Treatment
 - Control of hyperglycemia does not influence cutaneous involvement
 - No specific treatment available

Cutaneous Myxoma

- Clinical features
 - Papular lesion
 - May be seen in Carney complex (33% of patients)
 - Perifollicular in orientation
 - Includes subungual myxomas
 - Propensity for local recurrence if incompletely excised
- Pathology
 - Myxoid and variably cellular
 - Localized accumulation of mucin within the reticular dermis

CALCIUM DEPOSITS

Subepidermal Calcifying Nodule (Solitary Congenital Nodular Calcification, Winer's Nodular Calcinosis)

- Epidemiology: idiopathic (dystrophic calcification), most common in children
- Pathogenesis: trauma in utero, calcification of pre-existing milia, eccrine duct hamartoma, or nevi
- Clinical features
 - Solitary firm nodule
 - Most often found on head and neck, most common on ears
 - Lateral aspects of the digits
- Pathology: focal amorphous masses of calcium with inflammatory infiltrate
- Treatment: surgical removal if lesions are symptomatic

Calciophylaxis (Fig. 8-15)

- Epidemiology: predominant in females and diabetics; patients with obesity and poor nutritional status at higher risk
- Pathogenesis
 - Necrosis of skin secondary to calcification and occlusion of small cutaneous arterioles
 - Associated with: chronic renal failure, hypercalcemia, hyperphosphatemia, an elevated calcium-phosphate product, and secondary hyperparathyroidism; common in patients with endstage renal disease (ESRD)
- Clinical features
 - Early lesions are violaceous reticulated patches
 - Bullae may develop with tissue necrosis and ulcer formation
 - Lesions are extremely painful
 - Lower extremities most common location (90%); proximal greater than distal, where body fat is most abundant
 - Mortality rate of calciophylaxis is reported to be as high as 60% to 80%; the leading cause of death is sepsis from infected, necrotic skin lesions
 - Calcium-phosphate product frequently exceeds 60 to 70 mg²/dL²
 - Laboratory tests for blood urea nitrogen and creatinine levels; calcium, phosphate, alkaline phosphatase, and albumin levels; parathyroid hormone level, and coagulation factors: prothrombin time (PT), activated partial thromboplastin time (aPTT), protein C, protein S, anticardiolipin, lupus anticoagulant, factor V Leiden, and homocysteine



FIGURE 8-15 Calciophylaxis. (Reprinted with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003, p. 1493.)

- Pathology: Calcium deposits within the walls of blood vessels, mixed inflammatory infiltrate; subcutaneous calcium deposits with lobular panniculitis and fat necrosis vascular microthrombi, epidermal necrosis
- Treatment
 - Supportive with appropriate wound care and surgical debridement
 - Serum calcium and phosphate concentrations must be brought to low-normal levels; aggressive wound care, parathyroidectomy, hyperbaric oxygen, low calcium dialysis and systemic corticosteroids with cimetidine

Osteoma Cutis (Cutaneous Ossification)

- Epidemiology
 - Equal incidence in men and women
 - Four genetic disorders that feature cutaneous or subcutaneous ossification:
 - Fibrodysplasia ossificans progressiva (FOP)
 - Progressive osseous heteroplasia (POH)
 - Plate-like osteoma cutis (POC)
 - Albright's hereditary osteodystrophy (AOH)
- Pathogenesis
 - Intramembranous ossification begins in the dermis
 - Familial occurrence of Albright's hereditary osteodystrophy (pseudohypoparathyroidism and pseudopseudohypoparathyroidism) may be present
- Clinical features
 - Face, extremities, scalp, digits, and subungual regions
 - POH is more progressive and has associated morbidity due to extensive ossification, lesions are symptomatic papules and nodules
 - POC has one or few areas of involvement, non progressive
 - AHO associated with pseudohypoparathyroidism and brachydactyly
- Pathology: mature bone is found in the dermis or extends into the subcutaneous tissue
- Treatment
 - Underlying abnormalities of calcium/or phosphorus should be addressed
 - Excision of the neoformed bone
 - Recurrence is common in genetic disorders that result in ossification of skin

Calcinosis Cutis (Cutaneous Calcification)

- Pathogenesis
 - Calcium deposits form in the skin
 - Insoluble compounds of calcium (hydroxyapatite crystals or amorphous calcium phosphate) are deposited within the skin

- Clinical features: four major types
 - Dystrophic: due to trauma, inflammatory processes, tumors, infections
 - Metastatic: abnormal calcium or phosphate metabolism
 - Iatrogenic: secondary to a treatment or procedure
 - Idiopathic: no causative factor identifiable
 - Ectopic calcification can occur in the setting of hypercalcemia and/or hyperphosphatemia (if calcium-phosphate product exceeds $70 \text{ mg}^2/\text{dL}^2$)
 - Multiple, firm, whitish dermal papules, plaques, nodules, or subcutaneous nodules
 - Laboratory studies: serum calcium, inorganic phosphate, alkaline phosphatase, and albumin
- Pathology: granules and deposits of calcium are seen in the dermis, with or without a surrounding foreign-body giant cell reaction
- Treatment: correct the underlying problem

Gout

- Epidemiology
 - More common in men
 - Patients with hypertension, diabetes, hyperlipidemia, chronic kidney disease, or the metabolic syndrome are at increased risk for developing gout
- Pathogenesis
 - Over 99% of cases associated with decreased renal excretion of uric acid
 - Rarely, overproduction of uric acid (*Lesch-Nyhan syndrome* with self-mutilation)
 - Secondary elevation in leukemia, polycythemia, hemolytic anemia, tumor chemotherapy; diuretics, chronic renal disease, and ketoacidosis (diabetes mellitus, fasting)
- Clinical features
 - Acute arthritis with exquisite pain, swelling; most often involves great toe (podagra) (60%), less often other digits (10%), feet (10%), or other joints. Renal stones a risk
 - Cutaneous findings include uric acid deposits (*tophi*) most often on ears or periarticular; differential includes rheumatoid nodule
- Pathology
 - Epidermis normal or ulcerated; large deposits of amorphous, basophilic material with parallel, needle-shaped clefts within the dermis and subcutis; lymphohistiocytic infiltrate, often with granulomatous foreign-body reaction
 - Fixation in 100% ethanol, crystals are birefringent; crystals dissolve if tissue fixed with formaldehyde; the fixation fluid can be tested for presence of urates

- Treatment: acute flares treated with NSAID or colchicine; prophylaxis with diet, probenecid or allopurinol

Hemosiderin

- Pathogenesis
 - Intradermal deposits of iron (hemosiderin), chemical degradation
 - Associated with hemorrhage (purpura, stasis dermatitis)
- Clinical features
 - Clinical: brown, reddish-brown macules, patches
 - Skin pigmentation in hemochromatosis is caused by epidermal melanin, but hemosiderin is present as well
- Pathology: siderosis around foreign bodies (Perl's iron stain)
- Treatment: focuses on limiting the effects of the underlying disease leading to continued deposition. In hemochromatosis, this entails frequent phlebotomy

PERFORATING DISORDERS

Kyrle's Disease

- Epidemiology
 - Adult onset
 - Occurs in up to 10% of dialysis patients
 - Usually in association with diabetes mellitus and/or pruritus of renal failure
 - Rarely occurs with the pruritus of liver disease or internal malignancy
 - May represent end stage of perforating folliculitis
- Pathogenesis
 - Increased fibronectin levels are found in diabetics and patients with uremia
 - Fibronectin binds to type IV collagen and keratinocytes and may incite epithelial proliferation and perforation
- Clinical features: occurs most commonly on the legs
- Pathology
 - Plug of crusting or hyperkeratosis with variable parakeratosis
 - Transepidermal elimination of elastic fibers and collagen
- Treatment
 - Phototherapy
 - Intralesional steroids
 - Oral/topical retinoids

Perforating Folliculitis

- Epidemiology: more common in women

- Clinical features
 - Onset in young adulthood
 - Primarily affects the trunk and extremities
 - May be ordinary folliculitis with follicular rupture
- Pathology: necrotic material extruded
- Treatment
 - Intralesional corticosteroids
 - Oral/topical retinoids

Elastosis Perforans Serpiginosa (EPS)

- Epidemiology
 - Begins during childhood or early adulthood
 - 40% of cases occur in association with genetic disorders, including
 - Down's syndrome
 - Ehler-Danlos syndrome
 - Osteogenesis Imperfecta
 - Marfan's syndrome
 - Pseudoxanthoma elasticum
 - Rothmund-Thompson syndrome
 - Cutis laxa
 - Acrogyria
 - Can be induced by penicillamine
- Clinical features
 - Keratotic 2–5 mm papules, arranged in a serpiginous pattern
 - Most commonly on the lateral neck, face arms and flexural areas
 - Minimal pruritus
- Pathology
 - Plug of hyperkeratosis + / – parakeratosis
 - Elastic fibers are seen within the plug or epidermis
 - If penicillamine induced, characteristic lumpy-bumpy elastic fibers with lateral buds seen in lesional and non-lesional skin
- Treatment
 - Inherited forms are often mild and don't require treatment
 - Local cryotherapy
 - Tangential excision
 - Electrosurgical destruction
 - Cellophane tape stripping

Reactive Perforating Collagenosis

- Epidemiology: rare
- Clinical features
 - Begins during childhood
 - After superficial trauma, patients develop keratotic papules over the following 3–4 weeks
 - Koebnerization can occur
 - Arms and hands most commonly involved
 - Tend to spontaneously resolve over 6–8 weeks
 - Rare familial variant: verrucous perforating collagenoma in which severe trauma triggers

the formation of verrucous papules with transepidermal elimination of collagen

- Pathology
 - Plug of hyperkeratosis with or without parakeratosis
 - Collagen fibers seen in the epidermis and in the plug
 - Dermal connective tissue adjacent to the plug is normal
- Treatment: Inherited form remains mild and rarely needs treatment

OTHER DISORDERS

Flegel's Disease (Hyperkeratosis Lenticularis Perstans)

- Epidemiology: AD or sporadic
- Pathogenesis: lamellar granule's (Odland bodies) are absent or altered on electron microscopy, which results in hyperkeratosis
- Clinical features
 - Numerous symmetric keratotic papules on the dorsal aspects of the feet and distal arms and legs, including the palms and soles
 - Attached scale, more prominent at periphery—removal may result in bleeding
 - Associated with endocrine disorders such as diabetes mellitus and hyperthyroidism
- Treatment
 - Topical 5-fluorouracil cream
 - PUVA with topical calcipotriol

Malignant Atrophic Papulosis (Degos Disease)

- Epidemiology: equal incidence in men and women; typically occurs between the 2nd and 4th decades
- Clinical features
 - Vaso-occlusive disorder that affects the skin, gastrointestinal tract and CNS
 - Skin lesions begin as crops of small 2–5 mm erythematous papules on the trunk or extremities that over 2–4 weeks evolve to have a central depression and porcelain white scar with a rim of telangiectasias
 - Skin findings usually precede systemic findings
- Pathology: wedge shaped area of altered dermis with a sparse perivascular lymphocytic infiltrate and atrophic epidermis
- Treatment: no proven treatment—consider pentoxifylline or aspirin

Anetoderma (Fig. 8-16)

- Epidemiology: more frequently in women aged 15–25 years



FIGURE 8-16 Anetoderma. (Reprinted with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003, p. 1028.)

- Clinical features
 - Primary anetoderma occurs when there is no underlying disorder—there are Two types
 - Jadassohn-Pellizzari type—with preceding inflammatory lesions
 - Schweninger-Buzzi type—without preceding inflammatory lesions
 - Secondary anetoderma occurs in the same site as a previous skin lesion or in association with underlying diseases (including HIV or antiphospholipid antibody syndrome)
 - Characteristic lesions are flaccid circumscribed areas of slack skin that are a reflection of markedly reduced or absent dermal elastic fibers—can appear as depressions, wrinkling or sac-like protrusions
 - “Buttonhole sign” present
 - Chest, back, neck and upper extremities are sites of predilection
 - Described in premature infants and possibly related to the use of cutaneous monitoring leads or adhesives

- Pathology: focal, complete loss of elastic tissue in the papillary and/or mid-reticular dermis
- Treatment: surgical excision in patients with limited lesions

Idiopathic Atrophoderma of Pasini and Pierini

- Epidemiology
 - Women to men 6:1
 - Starts insidiously during the 2nd or 3rd decade of life
- Pathogenesis: possible role for *Borrelia burgdorferi* (+ serology in 40–60%)
- Clinical features
 - Lesions appear on the trunk, especially the back and lumbosacral regions
 - Often symmetric and bilateral, but can appear along Blaschko's lines
 - The borders or edges are sharply defined with "cliff-drop" borders
 - Perilesional skin is normal
 - The course is progressive
- Treatment
 - No treatment has been proven effective
 - Penicillin has been used with inconclusive results
 - Q switched alexandrite laser for hyperpigmentation

Ainhum: Autoamputation of a Digit

- Epidemiology: triggered by trauma
- Pathogenesis: fibrotic band develops from a flexural groove and progressively encircles the toe until spontaneous autoamputation occurs
- Clinical features: most commonly the fifth toe
- Pathology: fissuring and epidermal hyperkeratosis and parakeratosis, followed by a fibrotic reaction under the deepening fissure; as scar tissue contracts, it constricts and narrows neurovascular bundles
- Treatment: no current treatment appears to halt the progression of ainhum

Pseudoainhum (Amniotic Band Syndrome)

- Epidemiology: may be acquired or congenital
- Pathogenesis
 - Due to a collagen band around the affected area;
 - Occurs as a secondary event resulting from certain hereditary and nonhereditary diseases leading to annular constriction of digits
 - Can occur after premature rupture of the amniotic membrane
- Clinical features
 - Ring-like constriction bands, presenting as circumferential grooves of variable depth on the digits, extremities, neck or trunk
 - Early in gestation can result in the body wall complex, characterized by body wall defects

with evisceration of thoracic and /or abdominal organs, irregular anencephaly/encephaloceles and bizarre facial clefting

- Treatment: plastic surgery to release bands

Pseudoxanthoma Elasticum (PXE) (Fig. 8-17)

- Epidemiology: AR; occurs in all races without geographic predilection and appears to have a slight female predilection
- Pathogenesis: inactivating mutations in the ABCC6 gene
- Clinical features
 - Affects the elastic fiber network of the skin, eyes and cardiovascular system
 - Discrete, flat, yellowish papules in the flexural areas appear in the 1st or 2nd decade of life, ("plucked skin appearance")
 - Lateral neck usually affected first
 - Mucosal involvement most prominent on the inner aspect of the lip
 - Angioid streaks of the eye, result from breaks in the calcified elastic lamina of Bruch's membrane, which result in neovascularization, hemorrhage and scarring and ultimately in progressive loss of visual acuity and rarely, legal blindness
 - Affects medium sized arteries, predominantly of the extremities
 - Frequent sequelae include intermittent claudication, loss of peripheral pulses, renovascular hypertension, angina pectoris and myocardial infarction



FIGURE 8-17 Pseudoxanthoma elasticum. (Reprinted with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003, p. 1504.)

- Calcified blood vessels of the gastric and intestinal mucosa may increase the propensity for rupture and hemorrhage leading to GI bleeding
- Pathology: calcified elastic fibers in the mid and reticular dermis
- Treatment
 - Reconstructive surgery for skin sagging
 - Ophthalmology referral
 - Regular exercise, weight control, avoidance of smoking and excessive alcohol, treatment of dyslipidemia and hypertension

Hypertrophic Osteoarthropathy (HOA)

Divided into primary (pachydermoperiostosis) and secondary (hypertrophic pulmonary osteoarthropathies) forms

- Epidemiology
 - Pachydermoperiostosis (PDP): autosomal dominant; accounts for 5% of all cases
 - Hypertrophic osteoarthropathy (pulmonary hypertrophic osteoarthropathy): associated with underlying cardiopulmonary diseases and malignancies
 - Digital clubbing and subperiosteal new bone formation
 - Associated with polyarthritis, cutis verticis gyrata, seborrhea, and hyperhidrosis
- Treatment: NSAIDs or corticosteroids may alleviate the polyarthritis associated with PDP

Dermatofibrosis Lenticularis Disseminata (Buschke-Ollendorf Syndrome)

- Epidemiology: AD
- Pathogenesis: mutation causes loss of function in LEMD3 gene
- Clinical features
 - Multiple skin-colored or slightly yellowish papules
 - Osteopoikilosis (stippled appearance to bones) represents islands of increased bone density
 - Nasolacrimal duct obstruction, amblyopia, strabismus, benign lymphoid hyperplasia, hypopigmentation, and short stature
- Pathology: poorly demarcated area of increased dermal collagen bundles in a haphazard array

Pseudocyst of the Auricle

- Epidemiology: middle-aged men
- Clinical features
 - Usually arises in the scaphoid fossa
 - Usually unilateral
 - Presents as a painless swelling and tends to arise over a course of a few weeks

- Pathology
 - Cavity within the auricular cartilage that contains clear fluid
 - Cartilage lining may show degenerative changes
- Treatment
 - Aspiration, with or without intralesional corticosteroids
 - Incision and drainage with destruction of the cavity

ULCERATION

Pressure Sores (Decubitus Ulcers)

- Epidemiology: common in elderly patients who are confined to hospital beds
- Pathogenesis
 - Prolonged immobility and recumbency
 - Vascular disease
 - Neurological disease causing diminished sensation
 - Malnutrition, severe systemic disease and general debility
- Clinical features
 - Occur in immobilized patients
 - Due to chronic pressure in tissues overlying bony prominences
 - Lumbosacral region, greater trochanters, and heels are the most common areas
 - Tissue ischemia and neural damage lead to necrosis
 - Varying degrees
 - I: erythema
 - II: induration, blisters
 - III: shallow ulcers
 - IV: deep necrosis of fat and muscle
 - V: bone destruction
 - Underlying a small skin defect, there can be vast necrosis of deep tissues and proliferation of granulation tissue
- Pathology: epidermal necrosis, subepidermal bulla, vascular proliferations, often secondary inflammation
- Treatment
 - Prevention: turning recumbent patients regularly
 - Treatment of malnutrition
 - Debridement.
 - Regular cleansing with normal saline or 0.5% aqueous silver nitrate
 - Antibacterial, absorbent dressings and semipermeable dressings such as Opsite, if there is no infection
 - Appropriate systemic antibiotic if an infection is spreading
 - Plastic surgical reconstruction may be indicated in the young when the ulcer is clean

QUIZ

Questions

- Which of the following ichthyoses is associated with atopy?
 - Ichthyosis vulgaris
 - Lamellar ichthyosis
 - X-linked ichthyosis
 - Ichthyosis linearis circumflexa
 - Ichthyosis bullosa of Siemens
- All of the following ichthyoses have an associated ocular finding *EXCEPT*:
 - Conradi-Hunerman syndrome
 - X-linked ichthyosis
 - Netherton syndrome
 - Sjogren-Larson syndrome
 - Refsum syndrome
- Which 2 of the following ichthyoses are associated with scarring alopecia?
 - CHILD syndrome
 - Keratitis-ichthyosis-deafness syndrome
 - X-linked ichthyosis
 - Conradi-Hunerman syndrome
 - Lamellar ichthyosis
- Which of the palmoplantar keratodermas has a predisposition for malignancy?
 - Mal de Meleda
 - Vohwinkel syndrome
 - Howel-Evans syndrome
 - Papillon-Lefevre syndrome
 - Unna-Thost syndrome
- Auditory testing is recommended for patients with which of the following palmoplantar keratodermas?
 - Richner-Hanhart syndrome
 - Vohwinkel syndrome
 - Howel-Evans syndrome
 - Papillon-Lefevre syndrome
 - Unna-Thost syndrome
- According to Griffith's classification of pityriasis rubra pilaris, which type is associated with HIV?
 - Type I
 - Type II
 - Type III
 - Type IV
 - Type V
 - Type VI
- The two most likely drugs to cause an actinic lichenoid drug eruption confined to sun-exposed areas are:
 - Beta-blockers
 - Gold
 - Quinidine
 - Quinine
 - HCTZ
 - Mepacrine
- Which of the following is associated with the Koebner phenomenon?
 - Lichen nitidus
 - Lichen striatus
 - Lichen planus
 - Lichen simplex
 - Benign lichenoid keratosis
- All of the following are associated with pruritus *EXCEPT*:
 - Grover's disease
 - Lichen planus
 - Pityriasis rosea
 - Pityriasis lichenoides
 - Lichen simplex
- Erythema gyratum repens is associated with all of the following *EXCEPT*:
 - Lung cancer
 - Lupus erythematosus
 - Rapid migration of erythema (up to 1 cm/day)
 - Trailing scale present on the inner aspect of the advancing edge
 - Wood-grain appearance
- Type I and type II acute angioedema is associated with all of the following *EXCEPT*:
 - Low C1q
 - Low C2
 - Low C4
 - Low C1-INH
 - Low C4 between episodes
- Which of the following are recommended for treatment of refractory chronic urticaria?
 - Colchicine
 - Montelukast
 - Dapsone
 - Epinephrine
 - Glucocorticoids
 - Antihistamines
- Urticarial vasculitis can be associated with each of the following *EXCEPT*:

- A. Connective tissue diseases
 - B. Lymphoreticular malignancies
 - C. Serum sickness
 - D. ACE inhibitors
 - E. Schnitzler's syndrome
 - F. Infectious mononucleosis
14. Which of the following is a major criterion of Sweet's syndrome?
- A. Lesions preceded by nonspecific respiratory or gastrointestinal tract infection
 - B. General malaise and fever
 - C. ESR > 20 mm/h
 - D. Abrupt onset of painful or tender erythematous plaques or nodules
 - E. Excellent response to treatment with systemic corticosteroids or potassium iodide
 - F. Histopathologic evidence of predominantly neutrophilic infiltration in the dermis with leukocytoclastic vasculitis
15. All of the following perforating disorders are associated with chronic renal failure *EXCEPT*:
- A. Reactive perforating collagenosis
 - B. Perforating folliculitis
 - C. Elastosis perforans serpiginosa
 - D. Kyrle disease
 - E. Calciphylaxis
16. Which test assists with the diagnosis of elastosis perforans serpiginosa (EPS)?
- A. Verhoeff-van Gieson stain
 - B. Perl's iron stain
 - C. Alizarin red stain
 - D. Congo red stain
 - E. Kveim test

Answers

1. A and D. Both ichthyosis vulgaris and ichthyosis linearis circumflexa are associated with atopic dermatitis. None of the other diseases listed have any known association with atopy.
2. C. Netherton syndrome patients do not have ocular manifestations of disease. X-linked ichthyosis is associated with comma-shaped corneal opacities. Sjogren-Larson syndrome patients show "glistening dots" of the retina by 1 year of age. Refsum syndrome is associated with "salt and pepper" retinitis pigmentosa, night blindness, and cataracts. Conradi-Hunerman syndrome is associated with focal cataracts.
3. B and E. Keratitis-ichthyosis-deafness syndrome and lamellar ichthyosis are the 2 ichthyoses associated with scarring alopecia. CHILD syndrome patients have ipsilateral non-scarring alopecia. Conradi-Hunerman syndrome patients have patchy non-scarring alopecia. X-linked ichthyosis has no association with alopecia.
4. C. Howel-Evans syndrome is associated with an increased risk of esophageal cancer. None of the other PPK syndromes are associated with malignancy.
5. B. Vohwinkel syndrome is associated with high-frequency hearing loss and requires auditory testing. Patients with Papillon-Lefevre syndrome need referral to a dentist as they can have periodontitis with loss of teeth. Patients with Howel-Evans syndrome need further work-up for detection of esophageal cancer. Richner-Hanhart syndrome patients need a referral to a nutritionist for a low-phenylalanine/tyrosine diet as well as an ophthalmologist as they can develop corneal ulcers and blindness.
6. F. HIV is associated with type VI. Types I and II are associated with adult disease. Types III, IV, and V are associated with juvenile disease.
7. D and E. Quinine and thiazide diuretics are most likely to cause an actinic lichenoid drug eruption. The other drugs listed are medications associated with lichenoid drug eruptions in general.
8. A. Lichen nitidus is the only one associated with the Koebner phenomenon. Lichen planus is associated with hepatitis C virus infection and Wickham striae. Lichen simplex is associated with prurigo nodularis of Hyde.
9. D. Both the acute (PLEVA) and chronic (PLC) forms of pityriasis lichenoides are non-pruritic. All other disorders listed have pruritus, which can be especially severe in lichen simplex.
10. D. Trailing scale on the inner aspect of the advancing edge is associated with erythema annulare centrifugum. All other answer choices are true for erythema gyratum repens.
11. E. C4 may be normal between angioedema episodes. All other answer choices are true.
12. A and C. Colchicine and dapsone are recommended for refractory urticaria. All other answer choices can be used for treatment of chronic urticaria, but are not the drugs of choice for refractory cases.
13. B. Lymphoreticular malignancies are associated with acute urticaria, not urticarial vasculitis. All other choices are associated with urticarial vasculitis. Schnitzler's syndrome is urticarial vasculitis associated with fever, hepatosplenomegaly, bone pain with osteosclerosis, sensorimotor neuropathy, lymphadenopathy, and monoclonal IgM.
14. D. Answer choice F resembles the other major criterion except that histologically there is no associated leukocytoclastic vasculitis in Sweet's syndrome.

Answers A, B, C, and E are all minor criteria. To make the diagnosis of Sweet's syndrome, the patient must fulfill 2 major and 2 minor criteria.

15. C. Elastosis perforans serpiginosa (EPS) has no known association with chronic renal failure. EPS can be associated with inherited fibrous tissue abnormalities, D-penicillamine, or idiopathic etiologies. A, B, and D can be associated with chronic renal failure. Answer choice E is not a perforating disorder but is common in patients with end-stage renal disease.
16. A. Acid orcein-Giemsa, adlehyde fuchsin, and Verhoeff-van Gieson stains are used to diagnosis EPS. Perl's iron stain is used to detect hemosiderin deposition. The alizarin red stain can be used to diagnose pseudoxanthoma elasticum (PXE). PXE can also be diagnosed with Verhoeff-van Gieson stain (choice A). Congo red stain shows green birefringence in colloid milium. The Kveim test is the most specific test for sarcoidosis where intradermal injection from the spleen or a lymph node of a patient with sarcoidosis is biopsied in 4–6 weeks to examine histologically for noncaseating granuloma formation.

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PIGMENTARY DISORDERS

JASON H. MILLER
ASRA ALI

MELANOCYTES

- Epidermal melanocytes are dendritic cells
- Provide melanin for 36 neighboring basal and spinous layer keratinocytes
- Number and distribution are the same in all skin types
- Production and distribution/retention of melanin causes different skin colors
- Types of melanin:
 - *Phaeomelanin*: red-yellow
 - *Eumelanin*: brown-black
- Melanosomes
 - Membrane-bound spherical organelles, site of melanin synthesis and storage
 - Found in melanocytes; they move from melanocytes to keratinocytes = epidermal melanin unit
- Types of melanosomes:
 - *Eumelanosomes*: large, elliptical in shape and contain organized fibrillar glycoprotein matrix needed for eumelanin synthesis
 - *Pheomelanosomes*: smaller, spherical in shape, loose fibrillar glycoprotein matrix
 - Four stages of maturation:
 - *Stage I melanosomes (premelanosomes)*
 - ▲ Found in the cytoplasm of melanocytes
 - ▲ Amorphous matrix; contain unprocessed glycoprotein
 - *Stage II melanosomes*
 - ▲ Found in the cytoplasm of melanocytes
 - ▲ Round or oval, with longitudinally oriented filaments
 - ▲ Contain tyrosinase
 - ▲ No active melanin synthesis in eumelanosomes; melanin synthesis (not melanogenesis) in pheomelanosomes
 - *Stage III melanosomes*
 - ▲ Found in the cytoplasm or dendrites of melanocytes
 - ▲ Round or oval, electron dense, melanin on the internal filament network
 - ▲ Tyrosinase activity becomes positive
 - ▲ Melanization begins at this stage
 - *Stage IV melanosomes*
 - ▲ Found in the cytoplasm or dendrites of melanocytes
 - ▲ Round or oval, electron opaque
 - ▲ Fully melanized
 - ▲ Possess melanin, no enzymatic activity
- Tyrosinase
 - Cofactor: copper (Cu^{2+})
 - Catalyzes two reactions
 - Hydroxylation of tyrosine to dopa (dihydroxyphenylalanine)
 - Oxidation of dopa to dopaquinone

PIGMENTED LESIONS

Melasma (Fig. 9-1)

- Increased number of melanocytes, increased melanized melanosomes
- Genetic and hormonal influences in combination with UV radiation
- May be precipitated by the following: oral contraceptive pills, pregnancy thyroid dysfunction, cosmetics, phototoxic or photoallergic drugs
- Clinical findings
 - Brownish hyperpigmented macules and patches, can be confluent or punctate
 - Most commonly seen centrofacial/malar/mandibular distribution
 - Depth may be epidermal, dermal, or mixed

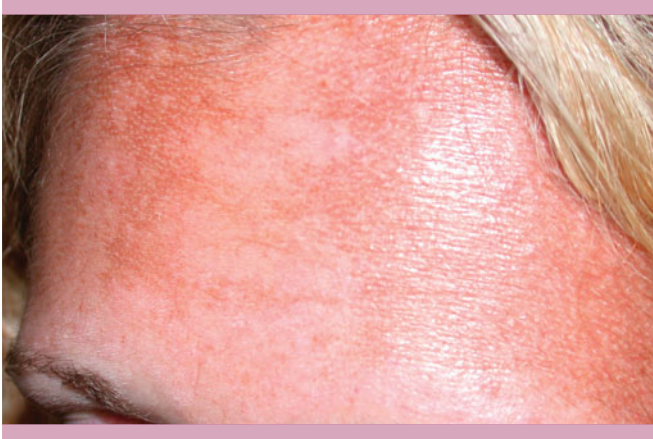


FIGURE 9-1 Melasma. (Courtesy of Dr. Asra Ali.)



FIGURE 9-2 Becker's nevus. (Courtesy of Dr. Asra Ali.)

- Diagnosis
 - Wood's light (wavelength, 340 to 400 nm): locates pigment; epidermal pigment enhanced, dermal pigment is not
- Treatment
 - Sunscreen, hydroquinone, tretinoin, chemical peels/microdermabrasion, azelaic acid, compounded agents (steroids, retinoids, hydroquinones), kojic acid, lasers (intense pulsed light, 1064-nm Q-switched Nd:YAG)

Becker's Nevus (Fig. 9-2)

- Acquired lesion in adolescents, most commonly on the scapular area of the back
- Normal number of basal melanocytes, increased epidermal melanotic hypermelanosis with increased melanin in the basal cell layer

- Increased number of testosterone receptors found in the lesion
- Clinical findings
 - Large, focal, brown, hair-bearing verrucous plaque
 - Back, shoulder, submammary areas are common
 - Associated with underlying musculoskeletal abnormalities (smooth muscle hamartomas, ipsilateral limb hypoplasia) and cutaneous hypoplasias
- Histology
 - Normal number of melanocytes with increased melanin pigment of basal layer, mature hair follicles with increased arrector pili muscles, thick bundles of smooth muscles
- Treatment
 - Surgical excision, laser hair removal

Congenital Nevomelanocytic Nevus (CNN) (Fig. 9-3)

- Presence of a pigmented lesion is noted at birth or soon thereafter
- Categorized by size:
 - Small (< 1.5 cm in diameter)
 - Medium (1.6 to 19.9 cm)
 - Large or giant (> 20 cm in adolescents and adults or comprising 5% of the body surface area or greater in infants, children, and preadolescents):
 - Lifetime risk of developing a melanoma for patients with a large CNN is 6.3%
- Related physical findings
 - *Leptomenigeal melanocytosis/neurocutaneous melanosis*: giant pigmented nevi located on the head, neck, or posterior midline and/or with multiple satellite lesions may present with



FIGURE 9-3 Congenital nevus. (Courtesy of Dr. Asra Ali.)

concurrent involvement of meninges and/or central nervous system; can lead to a communicating hydrocephalus; symptoms: irritability, photophobia, papilledema, nerve palsies; diagnosis is made by contrast-enhanced MRI, most sensitive imaging method to document CNS metastases

- Diagnosis of CNN
 - Histology: epidermal nevomelanocytes, dermal nevomelanocytes in sheets, nests, cords and/or single cells around and within adnexal components
 - Dermoscopy: globular/cobblestone or reticular pattern
- Treatment
 - surgical excision if clinically indicated, chemotherapy for metastatic disease

Spitz Nevus (Spindle Cell Nevus)

- Benign, usually acquired proliferations of melanocytes
- 50% of cases occur in children younger than 10 years of age
- Usually located on the face and lower extremities
- rapid initial growth phase
- Clinical findings
 - Typically solitary dome-shaped red/brown papule with a smooth surface/face; may occasionally

present as widespread eruptive lesions or as grouped lesions (agminated)

- Red color due to ectatic blood vessels
- Pigmented spindle cell nevus of Reed: variant of Spitz nevus, usually in adolescent girls; dark brown or black papule on the thigh
- Histology
 - Spitz nevus: predominantly compound, junctional and intradermal lesions may be seen; large and/or spindle-shaped melanocytes, usually in nests with artifactual clefts; periodic acid Schiff-positive and diastase resistant eosinophilic globules (Kamino bodies or colloid bodies), and dermal inflammatory cell infiltrate
 - Pigmented spindle cell nevus of Reed: melanocytes are spindle shaped, vertically oriented, can extend down eccrine ducts and/or involve hair follicles
- Treatment
 - Excision (narrow to 5-mm margins, based on clinical factors and degree of atypia)

Blue Nevus (Fig. 9-4)

- Origin unknown
- Blue color due to Tyndall effect: preferential absorption of long wavelengths of light by melanin and the scattering of shorter wavelengths

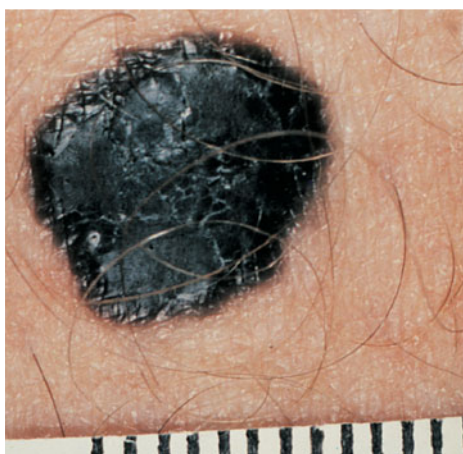
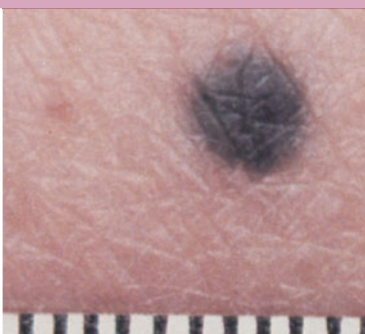
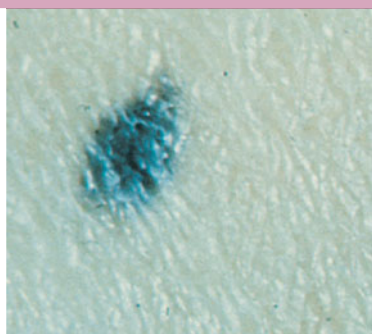


FIGURE 9-4 Blue nevus. (Reproduced with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th ed. New York: McGraw-Hill, 2003.)

- Clinical findings
 - Three main types of blue nevi:
 - *Common blue nevus*: blue-black papule, usually less than 10 mm in diameter, over 50% are found on the dorsa of the hands and feet
 - *Cellular blue nevus*: gray-blue solitary, larger than common blue nevus (usually 1–2 cm in diameter), usually smooth-surfaced papules; buttocks, the sacral region; malignant transformation of cellular blue nevi has been reported
 - *Combined*: blue nevus with a nevomelanocytic nevus; blue nevus may be either a common or cellular type with an associated overlying intradermal, compound, junctional, or Spitz nevus component
 - Malignant blue nevus may develop in relation to a cellular blue nevus; presents as a growing dermal nodule with or without ulceration
- Other physical findings
 - *Carney syndrome (complex)*: autosomal dominant, cardiac, cutaneous, and mammary myxomatous masses; lentigines, blue nevi, endocrine disorders, and testicular tumors
 - *LAMB syndrome*: lentigines, atrial myxomas, mucocutaneous myxomas, and blue nevi
 - *NAME syndrome*: nevi, atrial myxomas, myxoid tumors (neurofibromas), and ephelides
 - *Familial multiple blue nevi syndrome*: autosomal dominant, multiple lesions are present on the head and the neck, the trunk, the extremities, and the sclera, not associated with other cutaneous or systemic findings
- Histology
 - *Common*: dermal elongated, dendritic, finely pigmented melanocytes, Grenz zone usually separates the lesion from the epidermis
 - *Cellular*: two distinct cell types, dendritic melanocytes as in the common type, together with islands of plump, oval melanocytes with abundant cytoplasm, a round or oblong nucleus and central nucleolus, may extend into the subcutis with a diffuse or nested pattern.
 - *Combined*: macrophages with melanin, single dendritic melanocytes at the dermoepidermal junction with intraepidermal prolongations
 - *Epithelioid blue nevus*: majority of large- to medium-sized pigmented cells that are globular and polygonal (epithelioid), and a minority of cells that are spindled and dendritic
- Treatment
 - Simple excision

Café-au-Lait Macules (Fig. 9-5)

- Discrete, pale brown macules, smooth or irregular margins



FIGURE 9-5 Café-au-lait macules. (Courtesy of Dr. Jason Miller.)

- Appear at or soon after birth and may enlarge in size
- Isolated lesions occur in up to 20% of the population,
- Increased melanin in melanocytes and basal keratinocytes
- Associated diseases
 - Neurofibromatosis type 1 (seen in 95% of patients), also seen in McCune-Albright syndrome, tuberous sclerosis, Fanconi anemia (mental retardation, aplastic anemia, and risk for malignancy), Silver-Russel syndrome; Bloom's, Watson's, and Westerhof's syndromes; multiple endocrine neoplasia type IIb; Banyan-Riley-Ruvalcaba and Maffucci's syndromes;
 - McCune-Albright syndrome (Albright's syndrome): sporadic, *GNAS1* gene mutation (stimulates G protein, which increases cAMP), large café-au-lait macule with "coast of Maine" border, polyostotic fibrous dysplasia (pseudocysts of long bones), recurrent fractures, limb-length discrepancies, precocious puberty, hyperthyroidism, normal life span
- Treatment: not necessary, although can consider Q-switched laser (Nd:YAG, ruby) or intense pulsed light to lighten lesion, with variable response.

Nevus Spilus (Fig. 9-6)

- Presents during late infancy or early childhood
- Clinical findings
 - Circumscribed, lightly pigmented patch with darkly pigmented, speckled nevomelanocytic macules or papules
- Histology
 - Increased number of melanocytes in the tan background; flat dark areas resemble a lentigo



FIGURE 9-6 Nevus Spilus. (Courtesy of Dr. Jason Miller.)

with increased melanocytic hyperplasia or melanocytic dysplasia, collection of nevus cells are seen in the dark papular areas (junctional nevus)

Lentigo Simplex

- Acquired brown to dark variegated to uniformly colored macules
- Not induced by sun exposure and may occur anywhere on the skin
- Associated with the following syndromes
 - *Peutz-Jeghers syndrome* (see Chapter 32): autosomal dominant, oral pigmentation, benign gastrointestinal polyps
 - *LEOPARD syndrome*: lentigines, electrocardiographic conduction defects, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and deafness
 - *LAMB syndrome*: lentigines, atrial myxomas, mucocutaneous myxomas, and blue nevi
 - *Laugier-Hunziker syndrome*: oral pigmentation, nail hyperpigmentation, absence of intestinal polyps or systemic abnormalities
- Histology
 - Mild acanthosis and basilar hyperpigmentation with melanocyte proliferation
- Treatment
 - Cryosurgery: melanocytes freeze at -4 to -7°C , laser (Q-switched laser, intense pulsed light), tretinoin cream and hydroquinone, chemical peels

Cronkhite-Canada Syndrome

- Sporadically occurs
- Mutations of a tumor suppressor gene *PTEN* (phosphatase and tensin homologue deleted on chromosome 10)

- Most patients are older than age 50 at the time of presentation
- Clinical findings
 - Patchy alopecia, circumscribed hypermelanosis with lentigo-like macules on extremities, nail dystrophy
 - Sessile or semipedunculated polyps in the colon but also in the stomach and small intestine with malignant potential
- Histology
 - Increase in melanin within the basal layer without the melanocyte proliferation

Solar Lentigo

- Slowly increase in number and in size with increased ultraviolet light exposure
- Acquired lesions on sun exposed skin, most commonly seen in Fitzpatrick skin types I-III
- Lesions are light brown; ink spot lentigo: black in color
- Histology
 - elongated epidermal rete ridges with club-shaped extensions; increased numbers of epidermal melanocytes (no nesting)

Ephelides (Freckles)

- Occur on sun-exposed areas; common on central face and noted in early childhood
- Lesions appear in the summer months, may fade when sun exposure is decreased; may persist throughout life
- Light brown macules; color of the lesions tends to deepen after sun exposure
- Histology
 - increased melanin deposition in the basal layer

Nevocellular Nevus

- Benign neoplasms that are acquired after birth and composed of nests of melanocytes
- Stimulated by exposure to ultraviolet light, prevalence varies according to ethnicity-higher number of nevi in lighter skinned individuals
- Types of nevi
 - *Halo nevi*: occurs when nevus is attacked by immune cells; overall prevalence rate of 0.9%; usually occurs before age of 20 years; pink or brown central nevomelanocytic nevus surrounded by a symmetric round or oval halo of depigmented skin; may present with single or multiple lesions; when associated with melanoma, the central lesions usually appears atypical
 - *Junctional nevi* (Fig. 9-7): brown to brown/black macules, melanocytes are located at epidermal-dermal junction



FIGURE 9-7 Junctional nevus. (Courtesy of Dr. Asra Ali.)

- *Compound nevi*: papules, tan to light brown, melanocytes in dermis and at epidermal-dermal junction
- *Intradermal nevi*: papules display no melanin, melanocytes in dermis
- Histology
 - *Junctional nevus*: nevomelanocyte nucleus is pale staining and appears vacuolated; it is similar in size to epidermal melanocytes, cells have pale staining cytoplasm and are arranged in nests; the cells are separated from the normal epidermis by a space caused by retraction artifact
 - *Intradermal nevus*: cells progressively decreased in size from the epidermis to reticular dermis; grenz zone (area free of nevomelanocytes) may be present
 - *Balloon cell nevus*: histologic diagnosis; foam cells are present among the nevomelanocytes
 - *Recurrent melanocytic nevus* (pseudomelanoma): due to incomplete removal of a benign nevomelanocytic nevus; melanocytic hyperplasia, lentiginous pattern, atypia may be present
 - *Halo nevus*: central nevomelanocytes, dermal lymphocytic (mainly T cell) infiltrate and depigmented zone devoid of epidermal melanocytes

Dysplastic or Atypical Nevi

- Not a universally accepted term
- Originally known as Clark's nevi: clinically are asymmetric, with irregular borders, variegate in color

- Proportion of cutaneous melanomas that originate from dysplastic nevi relative to those that arise from apparently normal skin and from other melanocytic nevi is not known.

Familial Atypical Multiple Mole and Melanoma (FAMMM) Syndrome:

- Also known as the dysplastic nevus syndrome; germline mutations in the INK4alpha antioncogene encoding p16 in 40% of patients; increased risk for developing melanoma and other malignant neoplasms (i.e., pancreatic cancer)
- Presence of the following features: (1) occurrence of malignant melanoma in one or more first- or second-degree relatives, (2) presence of numerous (often > 50) melanocytic nevi, some of which are clinically atypical, (3) many of the associated nevi show certain histologic features and have an elevated lifetime risk for the development of melanoma
- Histology
 - Single melanocytes, elongation of rete ridges, with cytologic atypia of melanocytes and enlarged, hyperchromatic nuclei
 - Bridging: melanocytes aggregate into variably sized nests, which fuse with adjacent rete ridges
 - Dermal fibroplasia: lamellar and concentric, lymphocytic infiltrate
 - Shouldering: junctional component extends beyond the last dermal nest

Nevus of Ota (Nevus Fuscocaeruleus Ophthalmomaxillaris) (Fig. 9-8)

- Melanocytes that have not migrated completely from the neural crest to the epidermis during the embryonic stage
- Asian population most commonly affected, usually congenital
- Malignant melanoma has been reported to develop in a nevus of Ota
- Clinical findings
 - Blue to gray speckled macules or patches
 - Unilateral (90%). Can be bilateral (may appear similar to Hori nevus: acquired bilateral blue/gray macules, no mucosal involvement)
 - Forehead, temple, malar area, or periorbital skin; mucosal involvement is possible and may involve the sclera, conjunctiva and tympanic membrane (oculodermal melanocytosis); increased risk of glaucoma (10%)
- Histology
 - Dendritic melanocytes are present and surrounded by fibrous sheaths; dermal melanophages, five types based on the locations of the dermal melanocytes, which are (1) superficial, (2) superficial dominant, (3) diffuse, (4) deep dominant, and (5) deep

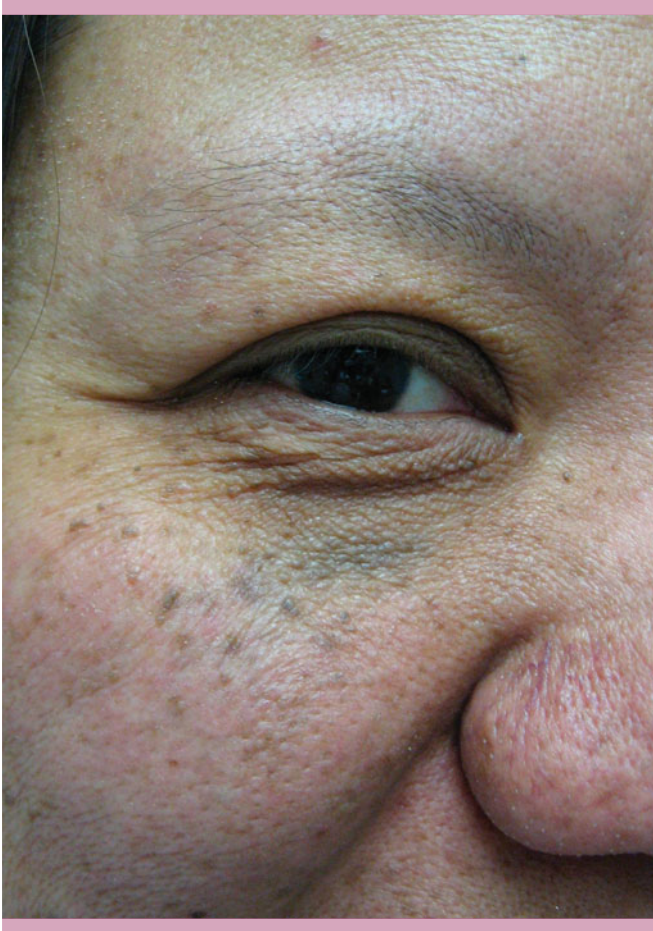


FIGURE 9-8 Nevus of Ota. (Courtesy of Dr. Jason Miller.)

- Treatment
 - Q-switched: alexandrite, Nd:YAG, ruby lasers
- Prognosis
 - If untreated, lesions remain for life

Nevus of Ito (Nevus Fusco-Caeruleus Acromiodeltoideus) (Fig. 9-9)

- Congenital, blue to gray speckled macules or patches, lesions are present over the shoulder girdle region
- May appear simultaneously with nevus of Ota
- Histology, treatment, and prognosis is similar to nevus of Ota

Mongolian Spot [Congenital Dermal Melanosis (CDM)]

- Common in the following ethnic groups: Asian, African, and Hispanic
- Entrapment of melanocytes in the dermis during their migration from the neural crest into the epidermis
- Clinical findings: blue-gray macules, most commonly seen on lumbosacral skin, buttocks;

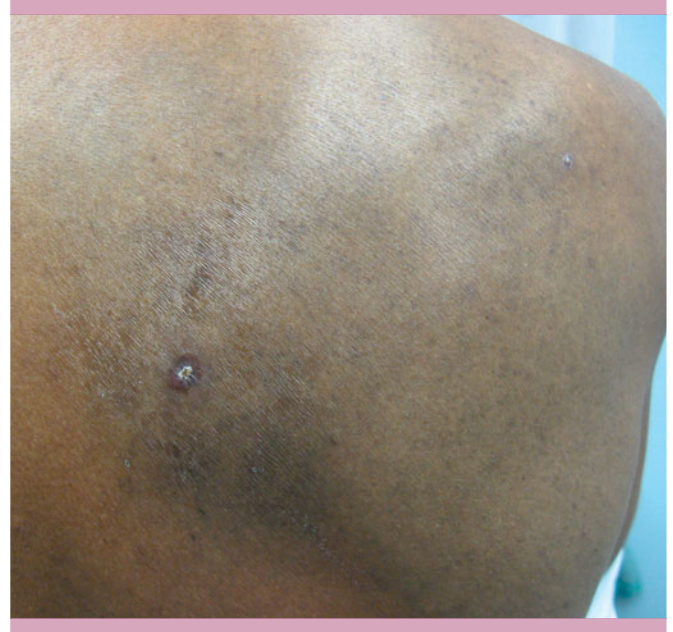


FIGURE 9-9 Nevus of Ito. (Courtesy of Dr. Jason Miller.)

other areas include thorax, abdomen, arms, legs, and shoulders

- Histology
 - Dermal spindle-shaped melanocytes with fully melanized melanosomes; usually oriented parallel to the epidermis
- Prognosis
 - Regression during childhood is the typical course, but they can persist

Dowling-Degos Disease (DDD/Reticulate Pigmented Anomaly of the Flexures)

- Autosomal dominant, mutation of the keratin 5 gene on chromosome 12q
- Clinical findings
 - Reticular, macular hyperpigmentation
 - Initially affects axillae and groin, other flexural areas
 - Comedo-like lesions and pitted acneiform scars near angle of mouth, neck, and back
 - *Galli-Galli disease (GGD)*: acantholytic variant of Dowling-Degos disease, clinically indistinguishable from DDD
- Histology
 - Acanthosis, irregular elongation of thin branching rete ridges with a concentration of melanin at the tips, no increase in melanocytes, but increase in melanosomes
- Treatment
 - Erbium YAG laser
- Prognosis
 - Slowly progressive but not life-threatening

Other Reticulated Hyperpigmentation Disorders

CONFLUENT AND RETICULATED PAPILLOMATOSIS OF GOUGEROT AND CARTEUAD (CRP)

- Grayish blue plaques with peripheral reticulated pattern maybe a chronic condition
- Favors neck and upper trunk
- Treatment: antimycotic agents, tretinoin, antimicrobial agents (i.e., minocycline, erythromycin)

ERYTHEMA AB IGNE

- Net like pigment pattern due to heat injury (heating pads or laptops)
 - Treatment: ND: YA6, alexandrite lasers

DYSKERATOSIS CONGENITA

- Usually XLR but sometimes autosomal dominant or recessive
- DKC1 (dyskerin) – telomerase defect
- Reticulate hyperpigmentation, nail dystrophy, premalignant leukoplakia, epiphora (continuous lacrimation)

NAEGELI-FRANCESCHETTI-JADASSOHN SYNDROME

- Autosomal dominant – keratin 14
- Reticulate hyperpigmentation starts at age 2 and fades over time
- Hypohidrosis, heat intolerance, dental abnormalities, PPK with loss of dermatoglyphics

DERMATOPATHIA PIGMENTOSA RETICULARIS

- Autosomal dominant – keratin 14
- Persistent truncal reticulated pigment; nonscarring alopecia; onychodystrophy; absent dermatoglyphics with punctuate keratoderma in some

RETICULATE ACROPIGMENTATION OF KITAMURA

- Autosomal dominant
- Atrophic pigment over dorsal hands and feet; palmar pits

HYPOPIGMENTED LESIONS (TABLE 9-1)

Nevus Depigmentosus

- Occurs sporadically, congenital condition
- Decreased number of melanosomes in keratinocytes, reduced dopa activity, underdeveloped dendrites, defect in melanosome transfer (melanin remains in melanocytes instead of transferring to keratinocytes)
- Clinical findings
 - Unilateral well circumscribed irregular, oval, or round hypopigmented macular lesion

Nevus Anemicus (Fig. 9-10)

- Appears at birth in early childhood
- Defect at motor end plate of smooth muscle effector cells of blood vessels

TABLE 9-1 Hypopigmented Diseases and Defects

Disease	Defect
Albinism	Decreased melanin synthesis
Nevus depigmentosus	Melanosome transfer
Menkes kinky hair	Decreased tyrosinase activity
Cross syndrome	Decreased number of melanocytes
Tuberous sclerosis	Decreased number of melanocytes, decreased melanin synthesis, decreased melanosome size
Vogt-Koyanagi-Harada	Decreased melanocytes

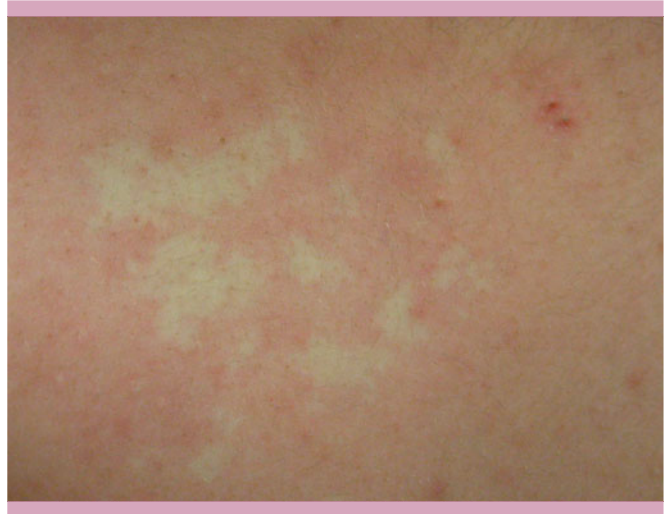


FIGURE 9-10 Nevus anemicus. (Courtesy of Dr. Asra Ali.)

- Focal area of blood vessel that have increased sensitivity to catecholamines; vessels are persistently vasoconstricted resulting in an area of cutaneous blanching
- Clinical findings
 - Well defined, hypopigmented, irregularly shaped, confluent macules forming a patch, most common on trunk; stroking the adjacent skin causes it to become erythematous, while the lesion remains pale in color

- Diagnosis:
 - *Dermoscopy*: obliterates border
 - *Wood's lamp*: no accentuation
 - *Histology*: normal epidermis, dermis, no changes in vasculature

Pityriasis Alba (Fig. 9-11)

- Melanocytes decreased in number with fewer and small melanosomes
- Commonly affects children
- Characterized as a mild form of atopic dermatitis
- Clinical findings:
 - Pale pink/light brown macules with indistinct margins, powdery scale: more apparent on darker skinned patients
- Treatment:
 - Topical steroids, emollients

Ash-Leaf Macules (See Chapter 32)

- Initial expression of tuberous sclerosis (seen in 90% of patients with TSC)
- Normal or decreased number of melanocytes with underdeveloped dendrites, and small, poorly melanized melanosomes
- Clinical findings:
 - Oval hypopigmented macules, posterior trunk, upper and lower extremities
- Histology
 - Mononuclear infiltrate concentrated in the area of hair follicles and sweat glands, absence of melanin



FIGURE 9-11 Pityriasis alba. (Courtesy of Dr. Asra Ali.)

Idiopathic Guttate Hypomelanosis (Fig. 9-12)

- Common, acquired, discrete hypomelanosis
- Usually on extremities of sun exposed skin
- Incidence increases with age
- Clinical findings
 - Discrete, well-circumscribed, porcelain white round macules
- Histology
 - Flattening of the dermal-epidermal junction, moderate to marked reduction of melanin granules and melanocytes in the basal layer, epidermal atrophy, hyperkeratosis
- Treatment
 - Cryotherapy, superficial abrasion, topical retinoids

Futcher's Lines (Voigt's Lines) (Fig. 9-13)

- Pigmentary demarcation lines
- Abrupt transitions from deeply pigmented skin to lighter-pigmented skin
- Often present at birth tend to darken with time
- More common in black population and becomes visible during the first 6 months of life, or may be apparent at birth becoming more noticeable with age or during pregnancy.
- Classification:
 - Based on location of lines of demarcation
 - a. Lateral aspects of upper anterior portion of the arms across pectoral area
 - b. Posteromedial portion of the lower limbs
 - c. Vertical hypopigmented line in the pre- and parasternal areas
 - d. Posteromedial area of the spine
 - e. Bilateral aspect of the chest, marking from the mid-third of the clavicle to the periareolar skin



FIGURE 9-12 Idiopathic guttate hypomelanosis. (Courtesy of Dr. Asra Ali.)



FIGURE 9-13 Futcher's lines (Voigt's lines).
(Reproduced with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th ed. New York: McGraw-Hill; 2003.)

HYPOMELANOSIS SYNDROMES

Vogt-Koyanagi-Harada (VKH) Syndrome (Uveomeningitic Syndrome)

- T-cell mediated autoimmune disorder; the autoimmune response might be triggered by an infectious agent in a genetically susceptible individual
- Clinical findings
 - Progression occurs in the following phases:
 - *Prodrome*: fever, malaise, headache, nausea, vomiting
 - *Meningocephalic*: meningeal symptoms with headache, meningismus, seizures, muscle weakness or paralysis
 - *Ophthalmic and auditory stage*: posterior uveitis, photophobia, altered visual acuity, eye

pain, retinal detachment, cataracts, glaucoma, dysacusis, deafness, tinnitus (50%)

- *Poliosis stage* (90%): symmetric vitiligo, white eyelashes and brows, alopecia

- Laboratory studies:
 - Cerebrospinal fluid: pleocytosis
- Treatment
 - High dose corticosteroids, cyclosporine, cyclophosphamide, chlorambucil, and azathioprine

OCULOCUTANEOUS ALBINISM (OCA)

- Autosomal recessive disorders caused by either a complete lack or a reduction of melanin biosynthesis in melanocytes resulting in hypopigmentation of the hair, skin and eyes
- The various types of OCA are caused by mutations in different genes (Table 9-2)

OCULOCUTANEOUS ALBINISM IA (OCA1)

- Autosomal recessive
- Mutated tyrosinase (*TYR*) gene, chromosome 11q
- Complete loss of tyrosinase function; no pigmented lesions
- Melanosomes are normal
- Clinical findings
 - Complete absence of melanin in skin, hair, eyes; “Albino” phenotype; white hair and skin, pink irides that turn blue-gray over time, decreased visual acuity, photophobia

OCULOCUTANEOUS ALBINISM IB

- Mutated tyrosinase (*TYR*) gene, with some tyrosinase function

TABLE 9-2 Types of Oculocutaneous Albinism (OCA)

Gene	Gene product	Disease name
<i>TYR</i>	Tyrosinase (TYR)	OCA1, OCA1A, OCA1B (<i>Yellow alb.</i>)
<i>OCA2 (p gene)</i>	OCA2	OCA2 (<i>Brown OCA in Africans</i>)
<i>TYRP1</i>	Tyrosinase-related protein 1 (TYRP1)	OCA3 (<i>Rufous OCA</i>)
<i>MATP</i>	Membrane-associated transporter protein (MATP)	OCA3 (<i>Rufous OCA</i>)

- Clinical findings
 - Develop varying pigment with age, hair with pheomelanin (spherical yellow melanosomes) resulting in light yellow to brown hair color, irides can turn light tan or brown, pigmented lesions can develop (nevi, freckles, lentigines)
 - *Temperature sensitive variant*: melanin synthesis in cooler areas of the body (i.e. extremities), but not warmer areas ($> 35^{\circ}\text{C}$)

OCULOCUTANEOUS ALBINISM II (OCA2)

- Autosomal recessive, tyrosinase positive
- “Brown” OCA
- Mutation in the OCA2 gene (previously *P* gene) (OCA2 protein is needed for melanosomes biogenesis and as a membrane transport protein); chromosome 15
- Most common OCA worldwide
- Clinical findings
 - Hair pigment present at birth (different from OCA I), yellow to blond at birth owing to pheomelanin, irides blue-gray, skin is creamy white at birth, does not tan, and does not develop further pigment, pigmented nevi may develop
 - Brown OCA type (variant of OCA2): seen in African/African American populations; skin and hair are lighter brown, irides gray to tan at birth; over time, hair and irides may darken, but skin remains the same
- Syndromes associated with OCA2 gene mutations:
 - *Prader-Willi syndrome*
 - Deletion of long arm of paternal chromosome 15 (imprinting) (70% of patients)
 - Developmental syndrome
 - ▲ Clinical findings
 - △ Neonatal hypotonia, hyperphagia and obesity, hypogonadism, small hands and feet, mental retardation, skin hypopigmented, no ocular albinism
 - *Angelman*
 - Autosomal recessive, defect in *OCA2* gene on maternal chromosome 15 (imprinting) Might represent a spectrum of OCA IB/OCA II
 - ▲ Clinical findings:
 - △ Light skin and hair, iris translucency, ocular albinism

OCULOCUTANEOUS ALBINISM III (OCA3)

- Autosomal recessive
- Mutation in tyrosinase-related protein 1 (*TRP1*) on chromosome 9
- Acts as a dihydroxyindole-2 carboxylic acid (*CDHICA*); oxidase needed in the eumelanin pathway
- Common in South Africa, can present as rufous/red OCA or brown OCA

- Clinical findings
 - Red to brownish skin, red hair, hazel to brown eyes

OCULOCUTANEOUS ALBINISM IV (OCA4)

- Defect in membrane associated transport protein (*MATP*) on chromosome 5
- Clinical
 - Similar to OCA II

Hermansky-Pudlak Syndrome (HPS)

- Autosomal recessive; etiology has been related to defects in 7 genes: *HPS1*, *HPS2* (*AP3B1*), *HPS3*, *HPS4*, *HPS5*, *HPS6*, and *HPS7*.
- HPS-1 patients have the most severe phenotype of HPS
- Lysosomal membrane defect with abnormal formation of intracellular vesicles; results in accumulation of ceroid lipofuscin in macrophages in lung and gastrointestinal tract
- Lack of platelet dense bodies resulting in increased bleeding times
- Tyrosinase positive
- Clinical findings
 - *Skin*: pigment dilution; skin color varies from white to light brown, pigmented nevi, ecchymosis
 - *Hair*: cream to red/brown
 - *Eyes*: lack of retinal pigment, decreased pigment of irides, photophobia, nystagmus, decreased visual acuity, strabismus
 - *Hematologic*: epistaxis, gingival bleeding, prolonged bleeding
 - *Lymphohistiocytic*: ceroid (chromolipid) deposition in macrophages
 - *Lung*: pulmonary fibrosis
 - *Gastrointestinal*: granulomatous colitis (15% of patients)
 - *Cardiac*: cardiomyopathy
- Diagnosis
 - Prothrombin time/partial thromboplastin time (PT/PTT)
 - Platelet count
 - Pulmonary function test, chest x-ray, and colonoscopy if symptomatic
- Treatment
 - Avoid aspirin and other blood thinners, DDAVP, platelet and red blood cell transfusions as clinically necessary; granulomatous colitis: steroids, TNF- α inhibitors

Chediak-Higashi Syndrome

- Autosomal recessive
- Lysosomal transport protein (*LYST/CHS1*) gene defect
- Incomplete oculocutaneous albinism

- Decreased chemotaxis of neutrophils, decreased antibody-dependent cellular cytotoxicity, presence of giant peroxidase-positive lysosomal granules in peripheral blood granulocytes; results in severe infections
- Clinical findings
 - Childhood CHS: accelerated phase: early onset with fever, anemia, neutropenia
 - Adolescent CHS: severe infections in early childhood, no accelerated phase
 - Adult CHS: mild form, develop progressive and fatal neurologic dysfunction in middle age
 - *Eyes*: ocular hypopigmentation causes photophobia, nystagmus, and strabismus
 - *Hair*: silvery sheen
 - *Skin*: pale, deep ulcerations, petechiae, bruising, gingival bleeding
 - *Neurologic*: seizures
 - *Lymphoma*: “accelerated phase” precipitated by viruses (e.g., Epstein-Barr virus); widespread infiltration of viscera
 - *Other*: hepatosplenomegaly, lymphadenopathy, pancytopenia, pseudomembrane, sloughing of the buccal mucosa
- Laboratory findings
 - Giant granules in circulating neutrophils, melanocytes, neurons, and renal tubular cells
 - Granules form secondary to delayed disorder of lysosomal enzymes from cells
- Treatment
 - Bone marrow (or stem cell) transplant, acyclovir, interleukin, gammaglobulin, vincristine, prednisone
- Course
 - Death at about 6 years old secondary to infection, lymphoma-like accelerated phase

Alezzandrini Syndrome

- Etiology unknown, possibly due to an autoimmune process destroying melanocytes
- Clinical findings
 - Facial vitiligo, poliosis, deafness, unilateral tapetoretinal (retinal pigmented epithelia) degeneration

Vitiligo (Fig. 9-14)

- Various theories on etiology of melanocyte destruction:
 - Autoimmune hypothesis: due to defects in humoral and cellular immunity
 - Neural theory: neurochemical mediator destroys melanocytes
 - Oxidant stress: accumulation of free radicals toxic to melanocytes, resulting in melanocyte destruction
- Associated with autoimmune conditions: thyroid disease (Hashimoto’s thyroiditis, Graves disease), diabetes mellitus, pernicious anemia, alopecia



FIGURE 9-14 Vitiligo. (Courtesy of Dr. Asra Ali.)

areata, Addison’s disease, psoriasis and multiple endocrinopathy syndrome

- Clinical findings
 - Depigmented, sharply circumscribed macules or patches
 - Poliosis = leukotrichia = whiteness of hair
 - Canities = premature graying of hair (37% of patients)
- Clinical classification
 - *Localized*: focal (one area of the body affected), segmental (dermatomal or quasidermatomal pattern), mucosal (mucous membranes are solely affected)
 - *Generalized*: acrofacial (distal fingers and periorificial affected), vulgaris (widely distributed scattered patches), mixed: acrofacial and vulgaris or segmental and acrofacial and/or vulgaris
 - *Universal*: complete or nearly complete depigmentation
- Diagnosis
 - *Wood’s lamp*: bright white or blue white
 - *Histology*: absence of melanocyte and melanin in the affected area
- Treatment
 - Narrow-band ultraviolet B, oral or topical psoralen plus UV-A (PUVA), topical calcineurin inhibitors, topical steroids; surgery: donor grafts: punch grafts, minigrafts, suction blister

Piebaldism

- Autosomal dominant
- *C-KIT* mutation on chromosome 4, encodes steel factor (*C-kit* ligand); protooncogene, tyrosine kinase

transmembrane cellular receptor for mast/stem cell growth factor.

- Present at birth, does not progress
- Clinical findings
 - *Cutaneous*: depigmented patches midforehead, extremities; pigmented islands present
 - *Hair*: white forelock (80% to 90% of patients)
 - *Gastrointestinal*: Hirschsprung disease
 - *Neurologic*: mental retardation, cerebellar ataxia, deafness

Waardenburg Syndrome

- Autosomal dominant
- Defect in neural crest migration, absent melanocytes
- Four subtypes (I to IV)
 - Type I : autosomal dominant, *PAX3* (paired box) gene; transcription factor
 - Type II: Autosomal dominant, *MITF* (microphthalmia-associated transcription factor) gene, chromosome 3; *SLUG* gene
 - Type III (Klein-Waardenburg syndrome): Autosomal dominant, *PAX3* (paired box) gene, transcription factor
 - Type IV (Shah-Waardenburg syndrome): Autosomal recessive, *EDN3* (endothelin receptor), *EDNRB*, G-protein coupled receptor;; Autosomal dominant, *SOX10* (sex determining region) gene
- Diagnostic criteria (Table 9-3):
 - WSI: two major or one major and two minor criteria

- WSII: two major criteria and dystopia canthorum instead of premature graying as one of the major criteria
- WSIII: two major or one major and two minor criteria along with musculoskeletal abnormalities
- Clinical findings
 - *Skin*: depigmentation
 - *Hair*: white forelock at birth (80%), synophrys (70%)
 - *Oral*: tooth caries
 - *Eyes*: heterochromia, dystopia canthorum (99%), lateral displacement of medial canthi with normal interpupillary distance; inner/outer canthi > 0.6
 - *Nose*: broad nasal root
 - *Ears*: congenital sensorineural deafness (20%)
 - *Gastrointestinal*: Hirschsprung disease (< 5%)
- Symptoms additional to main symptoms:
 - Type I: dystopia canthorum, heterochromia
 - Type II: heterochromia
 - Type III: musculoskeletal, limb abnormalities (hypoplasia, contracture of elbows, fingers)
 - Type IV: Hirschsprung's disease

QUIZ

Questions

1. A 40-year-old woman presents with a history of fever, seizures, photophobia, and poliosis of her eyebrows. The most likely explanation is:
 - A. New onset of generalized vitilgo
 - B. Molecular mimicry following a viral infection
 - C. Genetic abnormality in lysosomal trafficking
 - D. *PAX3* mutation
 - E. Cocaine use
2. The most common worldwide oculocutaneous albinism, presenting with yellow/blonde hair and pigmented nevi, occurs due to a mutation on which chromosome?
 - A. 17
 - B. 22
 - C. 15
 - D. 10
 - E. X
3. Axillary reticular hyperpigmentation with increased melanosomes and acantholysis on histology is most consistent with:
 - A. Cronkhite-Canada syndrome
 - B. Brooks-Spiegler syndrome
 - C. Tuberous sclerosis
 - D. Galli-Galli disease
 - E. Erythema ab igne

TABLE 9-3 Diagnostic Criteria for Waardenburg Syndrome

Major criteria	Congenital sensorineural hearing loss Pigmentary disturbances of iris; complete heterochromia iridis, partial or segmental heterochromia iridis, hypoplastic blue iridis White forelock Dystopia canthorum Affected first degree relative
Minor criteria	Congenital leukoderma: several areas of hypopigmentation Synophrys Broad and high nasal root Hypoplasia of ala nasi Premature graying of hair

4. A 14-year-old patient presents with numerous ephelides, blue nevi, and a history of endocrine abnormalities. Which of the following examinations should be ordered?
 - A. Skeletal survey
 - B. MRI of the brain
 - C. Duplex ultrasound of leg veins
 - D. Cardiac sonogram
 - E. Urinary metanephridines
5. Which of the following syndromes consists of abnormal pigmentary deposition without the presence of GI abnormalities?
 - A. Cronkhite-Canada syndrome
 - B. Peutz-Jeghers syndrome
 - C. Laugier-Hunziker syndrome
 - D. All of the above
 - E. None of the above
6. A 3-month-old infant presents with a 25×21 cm deeply pigmented patch over the central upper back, present since birth. Which is the most sensitive imaging study to identify potential leptomeningeal melanosis?
 - A. Contrast CT
 - B. Noncontrast CT
 - C. PET CT
 - D. Contrast MRI
 - E. Noncontrast MRI
7. Which of the following gene mutations has been associated with both an increase in inner canthal distance and gastrointestinal nerve plexus dysfunction?
 - A. SOX10
 - B. Pax3
 - C. MITF
 - D. endothelin 2
 - E. c-kit
8. An 8-month-old child presents with a silver sheen to her hair, seizures, hepatosplenomegaly, lymphadenopathy, pancytopenia, recurrent *Staph aureus* skin infections, and enlarged granules noted within neutrophils on peripheral smear. Which of the following gene defects is most likely to be identified?
 - A. c-kit
 - B. LYST
 - C. Pax3
 - D. HPS1
 - E. RAB27a
9. A 35-year-old woman, currently 30 weeks pregnant with her second child, presents with 2 months of worsening centrofacial hyperpigmentation that enhances upon Woods lamp fluorescence. This pigmentation was initially noted during her last pregnancy, but no treatment has yet been initiated. Which of the following would be the most appropriate initial treatment regimen?
 - A. Sunscreen and topical tretinoin
 - B. Sunscreen, topical tretinoin, and topical hydroquinone
 - C. Sunscreen alone
 - D. Sunscreen, topical hydroquinone, and topical steroids
 - E. Sunscreen and topical hydroquinone
10. Which of the following ions is necessary for the proper function of the enzyme tyrosinase?
 - A. Ca^{2+}
 - B. Mg^{2+}
 - C. Fe^{2+}
 - D. Fe^{3+}
 - E. Cu^{2+}

Answers

1. B. Vogt-Koynagi-Harada is a T-cell mediated autoimmune disorder that may be related to molecular mimicry following infection. Stages include a prodrome, ophthalmic and auditory stage, and poliosis stage.
2. C. Oculocutaneous albinism type 2 is the most common form worldwide and represents a tyrosinase positive albinism. Mutations in the OCA 2 gene (P gene) on chromosome 15 disrupt melanosome transport.
3. D. Galli-Galli disease is an acantholytic variant of Dowling-Degos disease, characterized clinically by reticulate hyperpigmentation and comedo-like lesions with pitted scars.
4. D. Carney complex consists of an autosomal dominant syndrome featuring lentigines, blue nevi, endocrine disorders, testicular tumors, and myxomatous masses of the heart, skin, and breasts. A cardiac sonogram would be useful in identifying atrial myxomas.
5. C. Laugier-Hunziker syndrome presents with oral and genital lentigines without the presence of GI polyps. Peutz-Jeghers syndrome consists of oral and genital lentigines with GI hamartomatous polyposis. Cronkhite-Canada syndrome presents with nail atrophy, alopecia, pigment deposition, digital melanotic macules, and GI polyps (premalignant).
6. D. A contrast-enhanced MRI is the most sensitive imaging study to identify melanosis or melanoma

- metastasis in the central nervous system. Clinical signs and symptoms may include irritability, photophobia, seizures, and hydrocephalus.
7. A. Waardenburg syndrome type IV consists of dystopia canthorum and Hirschsprung disease, likely due to neural crest developmental abnormalities. Associated mutations include SOX10 and endothelin-3 genes. Types I–III do not develop Hirschsprung disease. C-kit mutations are found in Piebaldism where, although Hirschsprung disease has been rarely reported, no dystopia canthorum would be noted.
 8. B. Chediak-Higashi syndrome consists of an autosomal recessive mutation in the *LYST* gene resulting in abnormal microtubule-associated lysosomal trafficking. Features include hair with a silver sheen, pigmented nevi, infections (staph aureus of the skin and pneumonia), ecchymoses, lymphoma (accelerated phase), neurologic degeneration, and pancytopenia. Neutrophils will characteristically show giant granules on smear.
 9. C. This patient presents with melasma that will likely require treatment in the future. However, as the patient is currently pregnant, the safest modality of treatment at this time consists of sunscreens alone. Topical hydroquinone and topical tretinoin are both FDA category C during pregnancy and would best be reserved until after parturition and lactation are complete.
 10. E. Copper is a necessary cofactor for the function of tyrosinase, an enzyme that catalyzes the hydroxylation of tyrosine to dopa and the oxidation of dopa to dopaquinone.
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DISORDERS OF FAT

ASRA ALI

JENNIFER KREJCI-MANWARING

NEOPLASMS OF THE SUBCUTANEOUS FAT

Lipoma

- Most common benign mesenchymal tumor
- Nonpainful, round, mobile soft masses, with normal overlying skin
- Histology
 - Mature adipocytes arranged in lobules, forming a well circumscribed nodule surrounded by a thin, fibrous capsule
 - Thin strands of tissue intersect the sheets of adipocytes
- Histologic variants
 - Angiolipoma
 - lipoma with co-existing vascular proliferation
 - may be painful and usually arise shortly after puberty
 - Pleomorphic lipomas
 - Bizarre, multinucleated giant cells are admixed with normal adipocytes
 - occur predominantly in men 50 to 70 years of age
 - Spindle cell lipomas
 - Slender spindle cells admixed in a localized portion of regular-appearing adipocytes
 - Adenolipoma
 - Characterized by the presence of eccrine sweat glands in the fatty tumor
 - Often located on the proximal parts of the limbs
 - Intramuscular lipomas: lipomas that extend into skeletal muscle
 - Fibrolipoma: thick bundles of collagen in the lipoma
 - Sclerotic lipoma: thickened collagen bundles with few persisting adipocytes
 - Myxolipomas: stromal deposits of mucopolysaccharides
 - Myelolipomas: ectopic hematopoietic bone marrow elements
- Infarcted lipomas: necrotic fat surrounded by multinucleate histiocytic giant cells, lymphocytes, and extravasated erythrocytes
- Other types of lipomas
 - Chondroid lipoma
 - Females > males; subcutaneous fat, muscle of hips, extremities
 - Histology: eosinophils, vacuolated cells that resemble chondroblasts, arranged in sheets, cords, mucinous stroma (cartilage), scalloped nuclei
 - Myolipoma/lipoleiomyoma
 - Resemble large lipomas, abdomen, retroperitoneum, > 15 cm, slimy, yellow-white cut surface
 - Histology: biphasic: mature adipocytes with smooth muscle cells, no atypia
 - Angiomyolipoma/angiolipoleiomyoma
 - Usually in kidney; associated with tuberous sclerosis; can occur in skin (acral, elbows, ears); these are not associated with tuberous sclerosis; slow growing; asymptomatic
 - Histology: blood vessels, smooth muscle bundles, adipose tissue, vessels with thick walls
 - Hibernoma
 - Red-brown, mobile, brown fat, solitary, between scapulae, lower cervical/mediastinal (most common), axillary
 - Histology: vacuolated cells, large round central nuclei with prominent nucleoli, abundant eosinophilic, granular cytoplasm secondary to mitochondria (mulberry cell)
 - Lipoblastoma/lipoblastomatosis
 - Appears only in infants, first three years of life, > 12 cm, solitary subcutaneous mass, trunk, limbs
 - Two variants:
 - ▲ Benign (circumscribed lipoblastoma): subcutaneous, well demarcated

- ▲ Diffuse (lipoblastomatosis): deep-seated infiltrates of soft tissue and skeletal muscle
- Histology: mature adipocytes separated into small lobules by fibrovascular septa; filled with cytoplasmic fat vacuoles displacing the nucleus to periphery (signet ring)
- Liposarcoma
 - Most common soft tissue malignancy in adults; arises de novo; elderly; nonmobile; rapidly enlarging; causes pain by compression
 - Histology: well-differentiated pleomorphic adipocytes; enlarged nuclei in thickened septa; sclerosing; abundant dense and fibrillary collagen; myxoid: most common variant, mucinous stroma

Syndromes

- Dercum's disease/adiposis dolorosa: tender nodules, idiopathic, obese, postmenopausal women, arms, trunk, paraarticular
- Madelung's disease/benign symmetric lipomatosis (Fig. 10-1): upper trunk, proximal extremities, middle-aged men, alcoholics or those with liver disease; "horse collar" appearance: confluence on neck; laboratory abnormalities: hyperuricemia, decreased glucose tolerance



FIGURE 10-1 Symmetric lipomatosis. (Reprinted with permission from Wolff, K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- Familial lipomatosis: autosomal dominant; third decade of life; hundreds of discrete nodules, slowly asymptomatic, extremities, forearms, intraabdominal
- Congenital lipomatosis: first few months of life; large subcutaneous masses, chest; infiltrating lipomas permeate skeletal muscle; manifests in Proteus syndrome (partial gigantism, autosomal recessive, hemi-hypertrophy, hemangiomas, lymphangiomas)
- Bannayan-Zonana syndrome (Bannayan-Riley-Ruvalcaba syndrome): autosomal dominant; multiple lipomas, syringomas, hemangiomas, macrocephaly, delayed motor and speech
- Treatment: surgical excision, liposuction

LIPODYSTROPHY

- Absence of subcutaneous adipose tissue with no evidence of inflammation, however, if previous inflammation was present, then the term lipoatrophy may be used
- Heterogeneous group of disorders defined by loss of subcutaneous adipose tissue and classified into two types: genetic and acquired.
- Associated with insulin resistance and its complications, such as impaired glucose tolerance, diabetes, hyperinsulinemia, dyslipidemia, hepatic steatosis, acanthosis nigricans, polycystic ovarian disease, and hypertension
- Congenital (recessive or autosomal dominant) disorders or acquired localized lipodystrophies (include drug-induced, pressure induced, panniculitis-associated, and idiopathic lipodystrophy)
- Histology: small adipocytes and intervening hyaline or myxoid connective tissue and proliferation of small blood vessels; second type has some inflammation with lymphocytes, foamy histiocytes, and plasma cells within the small fat lobules

Genetic Lipodystrophies

AUTOSOMAL RECESSIVE

1. Congenital generalized lipodystrophy (CGL; Berardinelli-Seip syndrome)
 - CGL type 1: AGPAT2 (1-acylglycerol-3-phosphate O-acyltransferase 2) mutations
 - CGL type 2: BSCL2 (Berardinelli-Seip congenital lipodystrophy 2) mutations
2. Lipodystrophy associated with mandibuloacral dysplasia
 - Partial lipodystrophy (type A pattern): LMNA (lamin A/C) mutations
 - Generalized lipodystrophy (type B pattern): ZMPSTE24 (zinc metalloproteinase) mutations
3. Lipodystrophy associated with SHORT syndrome (short stature, hyperextensibility, ocular depression, Reiger anomaly, teething delay)
4. Lipodystrophy associated with neonatal progeroid syndrome

AUTOSOMAL DOMINANT SYNDROMES

1. Familial partial lipodystrophy (FPL)
 - Dunnigan variety (FPLD): *LMNA* (lamin A/C) mutations
 - FPL associated with *PPARG* (peroxisome proliferator-activated receptor γ) mutations
 - FPL associated with *AKT2* (v-AKT murine thymoma oncogene homolog 2) mutations

OTHER VARIETIES

1. Lipodystrophy associated with Hutchinson-Gilford progeria syndrome (failure to thrive, scleroderma-like skin, limited growth, alopecia)
2. Pubertal-onset generalized lipodystrophy due to *LMNA* mutations
3. Generalized lipodystrophy (GL)
 - Berardinelli-Seip syndrome (Autosomal recessive)
 - Mutations in the following genes: type 1-AGPAT2 (1-acylglycerol-3-phosphate O-acyltransferase 2), band 9q34 and type 2-BSCL2 (Seipin), band 11q13
 - Diagnosis: Three major criteria or two major criteria and two or more minor criteria:
 - Major criteria: lipoatrophy affecting the trunk, limbs, and face; generalized lipoatrophy present at birth, insulin resistance with acanthosis nigricans, acromegaloid features, hypertriglyceridemia, hepatomegaly
 - Minor criteria: hypertrichosis, psychomotor retardation, hypertrophic cardiomyopathy, bone cysts, phlebomegaly
4. Acquired generalized lipodystrophy: (AGL)
 - Lawrence-Seip syndrome
 - Selective loss of body fat from large regions of the body occurring after birth
 - Three varieties: type 1, panniculitis variety (25%); type 2, autoimmune disease variety (25%); and type 3, the idiopathic variety (50%)
 - Characteristics: patients may have a voracious appetite, fatigue, acanthosis nigricans, hepatomegaly, fasting and/or postprandial hyperinsulinemia, diabetes mellitus, hypertriglyceridemia, and low serum levels of high-density lipoprotein cholesterol.
5. Partial lipodystrophy (PL)
 - Barraquer-Simons syndrome (Fig. 10-2)
 - Sporadic or autosomal dominant: *LMNB2* gene encodes Lamin B2
 - Loss of subcutaneous fat in demarcated symmetric areas of the body
 - Begins on the face and spreads downward, stopping at any level, often simultaneous fat hypertrophy of lower extremities
 - More common in females
 - Occasionally correlated with onset of an acute febrile illness
6. Familial partial lipodystrophy (FPL)
 - Associated with C3 nephritic factor (binds factor H) inhibitor of C3; results in uncontrolled activation of C3
 - Glomerulonephritis: direct toxicity from C3 nephritic factor
 - Histology: marked decrease or absence of subcutaneous fat cells
 - Treatment: renal transplant for increased uremia
7. HIV-associated lipodystrophy
 - Associated with highly active antiretroviral therapy (HAART); commonly associated medications include stavudine and to a lesser degree ziduvudine
 - Loss of subcutaneous fat of upper and lower extremities and from the face
 - Fat increases at the posterior neck and upper back and on the breasts



FIGURE 10-2 Partial lipodystrophy. (Reprinted with permission from Wolff, K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- Laboratory findings: insulin resistance and hyperglycemia
 - Treatment: changes within or between a class of HAART drugs, recombinant human growth hormone (rhGH), metformin, dehydroepiandrosterone, nonsteroidal anti-inflammatory drugs, liposuction of the upper back, filler substances (silicone, poly-L-lactic acid, calcium hydroxylapatite)
8. Other lipodystrophies/lipoatrophy
- Prior inflammatory processes involving the subcutis: lupus profundus, morphea, or panniculitis
 - Iatrogenic causes: subcutaneous injections of corticosteroids, insulin, or methotrexate
 - Subtypes of idiopathic lipoatrophies:
 - Annular lipoatrophy of the ankles: may be due to an inflammatory panniculitis that resolves with lipoatrophy; histology: mixed lobular panniculitis with lipophages
 - Lipoatrophia semicircularis: semicircular depressions of the anterolateral aspects of the thighs may be due to repeated mechanical trauma
 - Lipodystrophia centrifugal abdominalis infantilis: acquired localized lipodystrophy, mainly reported in Asians, loss of subcutaneous fat of the abdomen, slightly red and scaly skin in the surrounding area, lymphadenopathy, onset before age 5 years, and no significant associated diseases; histologically, loss of subcutaneous fat in the depressed area with panniculitis in the surrounding area.
 - Lesions last from 3 to 6 weeks and resolve with brownish/yellow discoloration (erythema contusiformis)
 - Chronic (EN migrans): several red subcutaneous nodules unilateral on the lower extremities
 - Etiologic factors: see Table 10-2
 - May also be *idiopathic*
 - Streptococcal infections are the most frequent etiologic factor for erythema nodosum in children, whereas drugs, sarcoidosis, and inflammatory diseases of the bowel are the most commonly associated disorders in adults
 - Diagnosis: biopsy, increased erythrocyte sedimentation rate, chest x-ray, complete blood count (CBC), antistreptolysin (ASO) titer, virologies, PPD for tuberculosis, fungal, bacterial and viral cultures
 - Histology: septal panniculitis without vasculitis; Miescher's radial granulomas: small, well-defined nodular aggregations of small histiocytes around a central stellate or banana-shaped cleft
 - Treatment: spontaneous resolution (3–6 weeks), nonsteroidal anti-inflammatory drugs (NSAIDs), oral steroids, potassium iodide

PANNICULITIS

- Group of heterogeneous inflammatory diseases that involve the subcutaneous fat
- Diagnosis using histology is essential since different panniculitides may show the same clinical appearance, which consists of erythematous nodules on the lower extremities
- Panniculitides are subdivided depending on the location of the inflammatory infiltrate: primarily lobular or septal (Table 10-1)

Panniculitis (Septal)

ERYTHEMA NODOSUM (EN) (FIG. 10-3)

- Most common type of septal panniculitis
- Most commonly affects young female patients
- Red or oval, slightly raised, nonulcerative painful red nodules, symmetric on the anterior surfaces of lower legs with fever, malaise, arthralgias (70%)

NECROBIOSIS LIPOIDICA

- Deep extension to the subcutis of the dermal process of palisading granulomas
- Asymptomatic, yellow-brown, indurated plaques with an atrophic and slightly depressed center and a well-defined raised erythematous edge
- Most commonly affects the bilateral shins symmetrically
- Associated with diabetes mellitus
- Histology: within the septa of adipocytes are histiocyte filled palisading granulomas surrounded by areas of degenerated collagen; IgM and complement depositions in the walls of the blood vessel of necrobiotic areas; dermis has alternating bands of inflammatory cells and fibrosis.
- Treatment: intralesional steroids, aspirin and dipyridamole, pentoxifylline

NECROBIOTIC XANTHOGRANULOMA

- Chronic and progressive, sharply demarcated indurated yellow to violaceous plaques commonly ulcerate, predilection toward the periorbital region
- Associated with paraproteinemia, mostly of IgG κ type, also found in patients with multiple myeloma
- Histology: large areas of necrobiosis (occasionally with cholesterol crystals in the center) alternating with granulomatous inflammation; occasional formation of lymphoid follicles
- Treatment: correct paraproteinemia, melphalan, prednisolone, plasmapheresis

TABLE 10-1 Panniculitis: Septal and Lobular

	Septal	Lobular
With vasculitis	(See Chap. 23) Leukocytoclastic vasculitis <ul style="list-style-type: none"> • Superficial thrombophlebitis • Cutaneous polyarteritis nodosa 	Erythema nodosum leprosum (see also Chap. 15) <ul style="list-style-type: none"> • Lucio's phenomenon (see also Chap. 15) • Nodular vasculitis (erythema induratum of Bazin) • Crohn's disease • Neutrophilic lobular (pustular) panniculitis associated with rheumatoid arthritis (not covered in this chapter)
Without vasculitis	<ul style="list-style-type: none"> • Erythema nodosum • Necrobiosis lipoidica • Necrobiotic xanthogranuloma • Rheumatoid nodule • Scleroderma/deep morphea • Subcutaneous granuloma annulare 	<ul style="list-style-type: none"> • α_1-Antitrypsin deficiency • Calciphylaxis • Cold panniculitis • Cytophagic histiocytic panniculitis • Subcutaneous "panniculitic" lymphoma • Factitial panniculitis • Iatrogenic • Infection • Lupus panniculitis (lupus erythematosus profundus) • Oxalosis • Pancreatic panniculitis • Poststeroid panniculitis • Sclerema neonatorum • Subcutaneous fat necrosis of newborn • Sclerosing panniculitis (lipodermatosclerosis) • Subcutaneous sarcoidosis • Traumatic • Panniculitis in dermatomyositis • Lipoatrophy (see previous section) • Gout panniculitis (patients with hyperuricemia may show urate crystal deposition in the fat lobule of the subcutis) • Crystal-storing histiocytosis (subcutis with aggregations of histiocytes containing crystalline deposits of immunoglobulins) • Postirradiation pseudosclerodermatous panniculitis (not covered)

RHEUMATOID NODULE

- Found in 20% of rheumatoid arthritis patients
- Usually asymptomatic firm nodules with normal overlying skin; predilection for the elbows and fingers
- Histology: large areas of necrobiosis (homogeneous and eosinophilic) surrounded by palisaded granulomas involving the dermis and subcutaneous fat
- Treatment: surgical excision if ulcerated or symptomatic

SCLERODERMA (DEEP MORPHEA, MORPHEA PROFUNDA)

- Extension from the deep dermis into the septa of subcutaneous fat; process can be entirely a panniculitis

- Bound down indurated plaques or nodules, heal with atrophy and residual hyperpigmentation
- Histology: extensive fibrosis of the septa of subcutaneous adipose tissue, collagen replaces fat normally present around the eccrine coils, atrophy of the adnexal structures, inflammation, with lymphocytes and plasma cells in active lesions
- Treatment: intralesional steroids, penicillamine

SUBCUTANEOUS GRANULOMA ANNULARE

- Subcutaneous nodules with a normal appearing skin surface; lesions are most often found on the head, hands, buttocks, and the anterior aspect of the lower legs



FIGURE 10-3 Erythema nodosum. (Reprinted with permission from Wolff, K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- Occurs most commonly in children and young adults
- Classic granuloma annulare can coexist 25% of the time with subcutaneous granuloma annulare
- Histology: necrobiosis with peripheral palisading granulomas involving the septa of adipose tissue

Panniculitis, Mostly Lobular With Vasculitis

ERYTHEMA NODOSUM LEPROSUM

- Type 2 reaction: Immune complex-mediated vasculitis in patients with lepromatous leprosy
- Painful erythematous and violaceous nodules, mostly involving the extremities
- Disease usually affects dermis only, but it can extend to the subcutis
- Histology: fibrinoid necrosis of vessel walls and luminal thrombi, direct immunofluorescence shows IgG and complement deposits in the vessel walls
- IgG and complement in the walls of the involved vessels
- Treatment: thalidomide, clofazimine, prednisone

LUCIO'S PHENOMENON

- Type 2 reaction: variant of lepromatous leprosy with hemorrhagic ulcers due to necrotizing vasculitis
- Histology: necrotizing vasculitis of the small vessels

with foamy histiocytes that contain numerous acid-fast bacilli

- Treatment: thalidomide

ERYTHEMA INDURATUM OF BAZIN (NODULAR VASCULITIS)

- Most common form of lobular panniculitis with vasculitis
- Erythematous, tender, subcutaneous nodules and plaques on posterior aspects of lower extremities
- May ulcerate and heal with atrophic scars, recurrence is common
- Usually seen in middle-aged women with venous insufficiency
- Erythema induratum of Bazin: if related to infection with *Mycobacterium tuberculosis* diagnosis can be made by Manoux test or by PCR for DNA of *M. tuberculosis*
- Histology: lobular panniculitis with vasculitis; ischemic necrosis of fat lobule with decreased septal involvement; tuberculoid-type granulomas, necrosis of adipocytes, foamy histiocytes, granulomatous infiltrate with epithelioid histiocytes, multinucleated giant cells and lymphocytes.
- Treatment: if *M. tuberculosis* is present, then nine months of antituberculosis triple-agent therapy is recommended, potassium iodide, treatment of venous insufficiency, NSAIDs to aid with pain of ulceration

CROHN'S DISEASE

- Abscesses, sinuses, and fistulas of the genital and perianal areas
- Commonly presents with erythema nodosum
- Histology: noncaseating granulomas composed of epithelioid histiocytes

Lobular Panniculitis Without Vasculitis

α_1 -ANTITRYPSIN DEFICIENCY (α_1 -PROTEASE INHIBITOR DEFICIENCY/SERINE PROTEASE)

- Affects homozygous patients; proenzyme of α_1 -antitrypsin is not released from the liver
- Alpha 1 antitrypsin is a protease inhibitor of trypsin (produced in liver), as well as the following: chymotrypsin, plasmin, thrombin, neutrophilic elastase, pancreatic elastase, serine proteases, collagenase, factor VIII, and kallikrein
- Clinical findings: cirrhosis, pancreatitis, emphysema, glomerulonephritis, vasculitis, acquired angioedema
- Panniculitis: lesions may occur after trauma; painful, recurrent nodules that drain a yellow fluid derived from fat breakdown; most commonly located on the lower extremities
- Diagnosis: serum α_1 -antitrypsin decreased
- Histology: fat necrosis with "skip areas" (areas of normal fat adjacent to necrotic adipocytes) or septal and lobular inflammation, splaying of neutrophils between collagen bundles of the reticular dermis in

TABLE 10-2 Etiologic Factors in Erythema Nodosum

Infections		Drugs	Malignancy	Misc.
Bacterial	Viral infections	Sulfonamides	Hodgkin's disease	Sarcoidosis
Streptococcal infections	Infectious mononucleosis	Bromides	Non-Hodgkin's lymphoma	Ulcerative colitis
Tuberculosis	Hepatitis B	Iodides	Leukemia	Colon diverticulosis
<i>Yersinia</i> infections	Milker's nodules	Oral contraceptives	Sarcoma	Crohn's disease
<i>Salmonella</i> infections	Orf	Minocycline	Renal carcinoma	Behçet's syndrome
<i>Campylobacter</i> infections	Herpes simplex	Gold salts	Postradiotherapy for pelvic carcinoma	Reiter's syndrome
Brucellosis	Measles	Penicillin		Sweet's syndrome
Tularemia	Cytomegalovirus infections	Salicylates		Pregnancy
Atypical mycobacterial infections	Fungal infections	Chlorothiazides		Takayasu's arteritis
Chancroid	Dermatophytes	Phenytoin		IgA nephropathy
Meningococcemia	Blastomycosis	Aminopyrine		Chronic active hepatitis
<i>Corynebacterium diphtheriae</i> infections	Histoplasmosis	Arsphenamine		Granulomatous mastitis
Cat-scratch disease	Coccidioidomycosis	Hepatitis B vaccine		Vogt-Koyanagi disease
<i>Propionibacterium acnes</i>	Sporotrichosis	Nitrofurantoin		Sjögren's syndrome
Shigella infections	Aspergillosis	Pyritinol		
Gonorrhea		D-Penicillamine		
Syphilis		Thalidomide		
Leptospirosis		Isotretinoin		
Q fever		Interleukin 2		
Lymphogranuloma venereum				
<i>Chlamydia psittaci</i> infections				
<i>Mycoplasma pneumoniae</i> infections				

Requena L, Yus ES. Panniculitis. Part I. Mostly septal panniculitis. *J Am Acad Dermatol* 2001 Aug;45(2):163-183.

early lesions; later lesions show fibrosis and a lymphohistiocytic infiltrate

- Treatment: avoid trauma, dapsone, supplemental infusion of exogenous alpha-1-protease inhibitor concentrate, liver transplantation

CALCIPHYLAXIS (SEE FIG. 8-15)

- Associated with chronic renal failure
- Calcification of cutaneous vessel walls causing necrosis and ulceration (see Chapter 8)

COLD PANNICULITIS

- Cheeks of children sucking ice cubes, ice packs, or popsicles
- Equestrian panniculitis: subtype of cold panniculitis; occurs in healthy women during cold months when riding horses and wearing tight trousers
 - Painful red nodules on superior lateral thighs develop 48 to 72 hours after exposure
- Indurated erythematous plaques with ill-defined margins
- Histology: lobular panniculitis, with lymphocytes and histiocytes in the fat lobules; edematous papillary dermis, perivascular lymphocytic infiltrate

Cytophagic Histiocytic Panniculitis

- May be part of a spectrum of disease with subcutaneous panniculitis-like T-cell lymphoma (see below)
- Presents with multiple subcutaneous nodules and plaques over limbs and trunk
- Non-fatal type has little/no systemic symptoms
- Histology: lobular panniculitis with lymphocytohistiocytic infiltrate with bean-bag cells (macrophages that phagocytize erythrocytes, leukocytes, or lymphocytes)
- Treatment: prednisone or cyclosporine

Subcutaneous “Panniculitic” Lymphoma

- High-grade aggressive lymphoma (most commonly cytotoxic T-cell) with appearance of panniculitis
- Persistent fever, hepatosplenomegaly, serosal effusions, pancytopenia and lethal hemorrhagic diathesis
- Histology: subcutaneous fat with pleomorphic lymphocytes large and hyperchromatic nuclei, karyorrhexis, and frequent atypical mitotic figures
- Immunohistochemical stains positive CD3, CD8, and cytotoxic granular proteins (TIA-1 and perforin); negative CD4
- Serologic and/or genotypic evidence of EBV infection

Factitial Panniculitis

- Self-inflicted: injections of foreign substances into the subcutaneous fat
- Histology: mostly lobular panniculitis; initially, inflammation mainly contains neutrophils and later, a more granulomatous infiltrate develops;

polarization may show the refractile foreign material; (sclerosing lipogranuloma: due to mineral oil injections, “swiss cheese” appearance with pseudocystic spaces in the subcutis surrounded by fibrotic tissue with foamy histiocytes and multinucleated giant cells)

Iatrogenic Panniculitis

- Drugs injected in the subcutaneous fat, such as povidone, meperidine, pentazocine, and vitamin K₁, or substances used to correct facial wrinkles, such as silicone, polymethyl-methacrylate (PMMA)-microspheres
- Histology: similar changes as seen with factitial panniculitis: mostly lobular panniculitis; early inflammation is primarily neutrophilic in and more granulomatous in late-stage lesions; polarization of the slide may identify the refractile foreign material; silicone injections show polygonal translucent angulated foreign bodies (impurities in the silicone) surrounded by multinucleated giant cells, foamy histiocytes are also present.

Infective Panniculitis

- Bacteria or fungi may cause lobular panniculitis mainly in immunosuppressed patients
- Local cutaneous infections with the following pathogens: *Streptococcus pyogenes*, *Staphylococcus aureus*, *Pseudomonas* spp, *Klebsiella*, *Nocardia* spp, atypical mycobacteria, *Mycobacterium tuberculosis*, *Candida* spp, *Fusarium* spp, *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Actinomyces israelii*, *Sporothrix schenckii*, *Aspergillus fumigatus*, and chromomycosis
- Due to:
 - Direct physical inoculation or from an indwelling catheter (primary)
 - Direct extension to the chest wall in pulmonary infections or hematogenous spread most commonly from the respiratory tract (secondary)
- Histology
 - *Primary cutaneous infections*: superficial dermis with inflammatory infiltrate; and thrombosed vessels void of the pathogenic organisms
 - *Secondary cutaneous infections*: epicenter of inflammation is found in deeper reticular dermis or subcutis; vessels are thrombosed, dilated, and contain organisms
- Diagnosis: culture of tissue and special stains of biopsy specimen
- Treatment: antimicrobial agents depending on the organism

Lupus Panniculitis (Lupus Erythematosus Profundus)

- One to three percent of patients with cutaneous lupus erythematosus

- May precede, appear simultaneously, or develop after systemic disease
- Trauma to subcutaneous fat can be a precipitating factor
- Deeply situated subcutaneous nodules or plaques on the upper arms, shoulders, face, and buttocks, overlying skin may show signs of chronic cutaneous lupus
- Atrophy after resolution
- Histology: 50% of patients with epidermal and dermal changes of discoid lupus erythematosus (epidermal atrophy, dermal-epidermal junction vacuolar changes, enlarged basement membrane, interstitial mucin, and superficial and deep perivascular lymphocytic infiltrate); the remaining cases have changes present only in the subcutis with a lobular panniculitis and a predominantly lymphocytic infiltrate, lymphoid follicles with germinal centers and peripheral plasma cells may also be found
- Immunofluorescence: linear deposition of IgM and C3 along the dermal-epidermal junction (lupus band)
- Treatment: systemic steroids or hydroxychloroquine

Panniculitis in Dermatomyositis (DM)

- May be present with cutaneous lesions of DM
- Tender, indurated plaques and nodules
- Histology: lobular panniculitis with lymphocytic and plasma cell infiltrate, fibrosis of adipocytes with fat necrosis and calcification
- Treatment: systemic steroids

Oxalosis

- Primary or secondary: both forms can cause renal failure
- Primary inherited oxalosis, autosomal recessive. Type I: 2-hydroxy-3-oxoadipate carboxylase deficiency; type II: deficiency of D-glyceric dehydrogenase.
- The cutaneous presentation of primary oxalosis is livedo reticularis and acral gangrene
- Secondary oxalosis
 - Excessive oxalate or glycolic acid ingestion, ethylene glycol poisoning, intravenous glycerol or xylitol infusion, methoxyflurane anesthesia, pyridoxine deficiency, intestinal disease, ileal resection, and in the setting of chronic renal failure, hemodialysis
 - Cutaneous involvement is more frequent in secondary acquired oxalosis
 - Miliary deposits of calcium oxalate on the palmar aspects of the fingers
- Histology: calcium deposition and yellow-brown oxalate crystals within and around vessels in deep dermis and subcutaneous tissue. In secondary oxalosis there is dermal calcium deposition with granulomatous inflammation surrounding it

- Treatment: renal transplant, for primary oxalosis-hepatic transplant should also be done to recover the deficient enzymes; prior to renal failure, serum alkalization may decrease oxalate formation

Pancreatic Panniculitis

- Associated with acute and chronic pancreatitis, 2% to 3% of all patients with other pancreatic diseases (such as pseudocysts, fistulas), and pancreatic cancer (mostly acinar cell type)
- Tender, fluctuant, erythematous subcutaneous nodules ulcerate spontaneously and exude an oily brown material (liquefaction necrosis of adipocytes)
- Pretibial area most common site, ankle arthralgias (may result from necrosis in periarticular fat tissue)
- Fat necrosis can occur internally (bone marrow fat, abdominal fat)
- Calcium precipitation can produce hypocalcemia
- Histology: ghostlike fat cells (thick cell wall, no nuclear staining, lobular, calcification), necrotic fat cells, polymorphous fat infiltrate
- Saponification: dystrophic calcification in ghost adipocytes (hydrolytic action of pancreatic enzymes on fat followed by calcium deposition)
- Treatment: resolution of the underlying pancreatic disease

Poststeroid Panniculitis

- Mainly in children who receive a short course of high dose systemic steroids with doses that were decreased quickly or steroid therapy was suddenly discontinued
- Deep nodules appear 1 to 10 days after cessation of steroid treatment; commonly seen on the cheeks
- Histology: lobular panniculitis with needle-shaped clefts (represent former sites of fatty acid crystals dissolved by tissue processing) within lipocytes, foamy histiocytes
- Prognosis: resolve with no complications; atrophic scars may result if ulceration occurs
- Treatment: reinstitution of steroid therapy with a gradual taper

Sclerema Neonatorum

- Develops during first few days of life
- Affects low weight debilitated premature newborns
- Greater ratio of saturated to unsaturated fatty acids than in adult fat
- Rapidly spreading induration of the skin; begins on buttocks to thighs, back; usually symmetric
- Histology: lobular panniculitis without fat necrosis, little inflammation, enlarged lipocytes with needle-like clefts (crystals of triglycerides), in a radial array

- Prognosis: poor, usually death within a few days

Subcutaneous Fat Necrosis of the Newborn (SFNN)

- Occurs in first 2–3 weeks of life in healthy full-term neonates
- Localized erythematous, violaceous, firm nodules and plaques; spares anterior trunk
- Greater ratio of saturated to unsaturated fatty acids compared to adults
- Hypercalcemia (unknown significance)
- Histology: granulomatous inflammation, lymphocytes, epithelioid cells, foreign-body giant cells, radially arranged needle-shaped clefts (crystals of triglycerides), fat in macrophages and giant cells, calcium deposition
- Prognosis: lesions regress spontaneously, may leave lipoatrophy
- Treatment: self limited, etidronate (for associated hypercalcemia)

Sclerosing Panniculitis (Lipodermatosclerosis, Hypodermatitis Sclerodermiformis)

- Indurated plaques with erythema, edema, telangiectasias, and hyperpigmentation involving the lower legs with a stocking distribution; resembles an “inverted wine bottle”
- Associated with chronic venous insufficiency, arterial ischemia, and previous episodes of thrombophlebitis
- Histology: stasis dermatitis changes (increased numbers of capillaries and venules in the papillary dermis, fibrosis, and deposition of hemosiderin), atrophy of the subcutaneous fat, late stages with lipomembranous changes (necrosis causes the formation of cystic spaces in the fat lobule that are lined with a homogeneous eosinophilic membrane with convoluted projections (stain brightly with periodic acid-Schiff and Sudan black and are resistant to diastase)
- Treatment: decrease venous stasis, stanozolol

Subcutaneous Sarcoidosis

- Subcutaneous nodules on the lower extremities without superficial cutaneous involvement
- Histology: noncaseating granulomas of the fat lobules and few lymphocytes at the periphery (“naked” granulomas); occasional calcification
- Treatment: systemic steroids

Traumatic Panniculitis

- Accidental blunt trauma, especially frequent in women with large breasts (excessive weight affects mammary subcutaneous fat)
- Mammary traumatic panniculitis: indurated nodules deeply situated on the breast tissue, surface of the

skin with occasional appearance of peau d’orange, may resolve with lipoatrophy

- Histology: cystic spaces within fat lobules, due to necrotic fat cells, surrounded by foamy histiocytes; fibrosis and hemorrhage may be present

Disorders Erroneously Considered as Specific Variants of Panniculitis

WEBER DISEASE

- Lobular panniculitis without vasculitis and systemic manifestations including fever and involvement of visceral fat tissue
- The term *Weber-Christian disease* was used as a diagnosis for cases of lobular panniculitis; however, now a more specific diagnosis may exist

ROTHMANN-MAKAI DISEASE

- Cases of relapsing nodular panniculitis without other systemic manifestations
- Obsolete term that is no longer used

LIPOMEMBRANOUS OR MEMBRANOCYSTIC PANNICULITIS

- Histopathologic pattern rather than a distinct disease
- Cystic spaces that form due to necrotic adipocytes in the fat that are lined with a homogeneous eosinophilic membrane with convoluted projections into the cystic cavity (positive for periodic acid-Schiff and Sudan black and diastase resistant).

EOSINOPHILIC PANNICULITIS

- Septal or lobular panniculitis in which eosinophils predominate in the inflammatory infiltrate; histopathologic pattern rather than a distinct disease
- Nonspecific reactive process found in many different disorders

QUIZ

1. A 40-year-old man presents with a tender mobile subcutaneous nodule. On biopsy, pathology shows a well circumscribed mass consisting of adipocytes with prominent vascular pattern with occasional thrombi. What is it?
A. Spindle cell lipoma
B. Angiolipoma
C. Liposarcoma
D. Pleomorphic lipoma
2. A 55-year-old man presented with an enlarging subcutaneous mass on his thigh. Wide excision revealed a delicate plexiform capillary network that is associated with both normal appearing lipocytes and lipoblasts with a myxoid stroma. What other location is this tumor found?

- A. Mediastinum
 - B. Head and neck
 - C. Acral
 - D. Retroperitoneum
3. A 38-year-old woman presents with loss of subcutaneous fat in her face and torso. She states that it has been progressive. What lab should you check?
 - A. Complete blood count
 - B. Protein electrophoresis
 - C. Urine analysis
 - D. Chest x-ray
 4. A 22-year-old female college student presents with tender erythematous nodules on her lower legs. She started a new medication 3 weeks ago. What is the next step in management?
 - A. Biopsy for H&E and fungal culture.
 - B. NSAID, rest, elevation
 - C. Colonoscopy
 - D. Throat culture
 5. A 68-year-old woman presents with a well demarcated yellow-brown plaque on her left cheek. Pathology reveals areas of necrobiosis with granulomatous inflammation and occasional cholesterol crystals. What is the most likely association?
 - A. IgG paraproteinemia
 - B. IgA paraproteinemia
 - C. Non-Hodgkin's lymphoma
 - D. Bilateral hilar infiltrates on chest x-ray
 6. A 53-year-old man from El Salvador with known lepromatous leprosy presents with tender violaceous nodules on his legs, fever, and arthralgias. What type of reaction is this?
 - A. Type 1
 - B. Type 2
 - C. Jarisch-Herxheimer
 - D. Lucio reaction
 7. A 60-year-old woman on hemodialysis develops dusky reticulated patches on her thighs that ulcerate and form eschars. Biopsy of the affected area would show?
 - A. Thrombi in small- and medium-sized vessels
 - B. Sheets of calcified dermis
 - C. Necrotizing vasculitis
 - D. Calcification of vessel walls
 8. You are asked to evaluate a full-term infant that was brought to the emergency room at 3 weeks of life. You see erythematous, violaceous, firm nodules and plaques on the back and buttocks. What is your diagnosis?
 - A. Sclerema neonatorum
 - B. Subcutaneous fat necrosis of the newborn
 - C. Erythema nodosum
 - D. Alpha-1-antitrypsin deficiency
 9. A 9-year-old boy is brought to your office in July for the onset of an ill-defined erythematous plaque on his left cheek. He is otherwise healthy but his mother says that he eats popsicles every day in the summer. What is your next step?
 - A. Biopsy
 - B. Topical corticosteroid
 - C. Reassurance
 - D. Warm compresses
 10. A 32-year-old man presents to your office with tender erythematous nodules on his lower legs. He has a scar on his lower abdomen and has chronic diarrhea. What other findings may be present?
 - A. Pyostomatitis vegetans
 - B. Posterior uveitis
 - C. Bilateral hilar infiltrates on chest x-ray
 - D. Recent treatment for UTI with trimethoprim/sulfamethoxazole

Answers

1. B. This is a pathologic description of an angiolipoma
2. D. This is a pathologic description of a liposarcoma. It is the most common soft malignancy in adults. It is most commonly found on the thighs, retroperitoneum and inguinal region.
3. C. This is acquired partial lipodystrophy which is associated with C3 nephritic factor. This binds factor H, an inhibitor of C3 and results in uncontrolled activation of C3 causing glomerulonephritis. They also have association with diabetes mellitus so you should check glucose or insulin levels.
4. B. This is erythema nodosum, likely occurring after the start of oral contraceptives. Given the history of the new medicine a biopsy is not necessary. EN is related to IBD but colonoscopy is not the best choice. In children, EN is related to strep pharyngitis. Supportive care is the best management in this case.
5. A. This necrobiotic xanthogranuloma. It is most commonly periocular and associated with IgG.
6. B. This is erythema nodosum leprosum which is a type 2 reaction usually in lepromatous leprosy. It is due to circulating immune complexes and treated with thalidomide. Type 1 reaction is a reversal reaction. Jarisch-Herxheimer reaction is seen in Lyme disease, syphilis after treatment with antibiotics. Lucio's reaction is due to mycobacterium invading vessels and is treated with rifampin.

7. D. This is calciphylaxis. The other answers are incorrect.
8. B. This is subcutaneous fat necrosis of the newborn because it is a full-term infant. Sclerema neonatorum occurs in premature infants. EN occurs in children but is usually related to strep pharyngitis and is found on the legs. Alpha-1-antitrypsin deficiency does not occur in this age group.
9. C. This is cold panniculitis likely induced by the child's fondness for popsicles. It should resolve with cessation of the offending agent and no treatment is needed.
10. B. This is erythema nodosum in the setting of inflammatory bowel disease, either Crohn's or UC. Pyostomatitis vegetans in an ulcer in of the oral mucosa with the characteristic "snail tracks." EN is also associated with sarcoid, Behçet's, and sulfa drugs, but these are not consistent with the given scenario.

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CUTANEOUS TUMORS

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SURFACE EPITHELIAL TUMORS

Seborrheic Keratosis (Fig. 11-1)

- Appearance: warty, sharply delineated, often scaly hyperpigmented plaques with greasy crust that appear “stuck on” the surface of the skin
- Location: trunk, shoulder, face, and scalp (areas with sebaceous glands), but can occur anywhere (except palms and soles)
- Demographics: > 30 years
- Histology: benign proliferation of epidermal keratinocytes that can be endophytic, exophytic, or flat. They contain horn pseudocysts (called “pseudo” because they connect to surface, and have no true epithelial lining) and are characterized by hyperkeratosis, papillomatosis, and acanthosis
- Syndrome
 - Leser-Trelat syndrome: sudden onset of numerous seborrheic keratoses associated with internal malignancies, most common adenocarcinoma of stomach, but also leukemia, lymphoma and other carcinomas
- Variants
 - Inverted follicular keratosis: verrucous, intradermal or “inverted” form of irritated seborrheic keratosis, arising in close approximation to a hair follicle, with prominent squamous eddies
 - Dermatitis papulosa nigra: multiple small, pedunculated, and heavily pigmented tag-like papules on the face of African-American and Afro-Caribbean patients (Fig. 11-2)
 - Stucco keratosis (keratosis alba): white-to-light brown (depigmented), flat keratotic lesions on dorsa of the feet, the ankles, and the dorsa of the hands and forearms

- Melanoacanthoma: deeply pigmented seborrheic keratoses in which an epidermal proliferation of large dendritic melanocytes is identified

Epidermal Nevus

- Appearance: yellowish-brown warty papules or plaques (Fig. 11-3)
- Location: usually on trunk and extremities
- Demographics: present at birth or develop during childhood
- Characterization: congenital hamartoma (nevus) of proliferating epidermis
- Three subtypes
 - Nevus verrucosus: solitary or multiple localized lesions
 - Nevus unius lateralis: extensive unilateral linear distribution
 - Ichthyosis hystrix: extreme involvement with bilateral or generalized distribution
- Histology: hyperkeratosis, papillomatosis, acanthosis, and elongation of the rete ridges
- Syndrome
 - Epidermal nevus syndrome: Skeletal, ocular, and central nervous system abnormalities
- Variations
 - Nevus sebaceus: see Sebaceous Tumors
 - Linear porokeratosis: see Porokeratosis
 - Linear epidermal nevus: usually present at birth; verrucous yellow-brown papules in a linear arrangement; systemic form follow Blaschko’s lines; heterozygous point mutation in the keratin 10 gene; histologically resemble nevus sebaceous that may show focal features of epidermolytic hyperkeratosis, lack dermal adnexal components

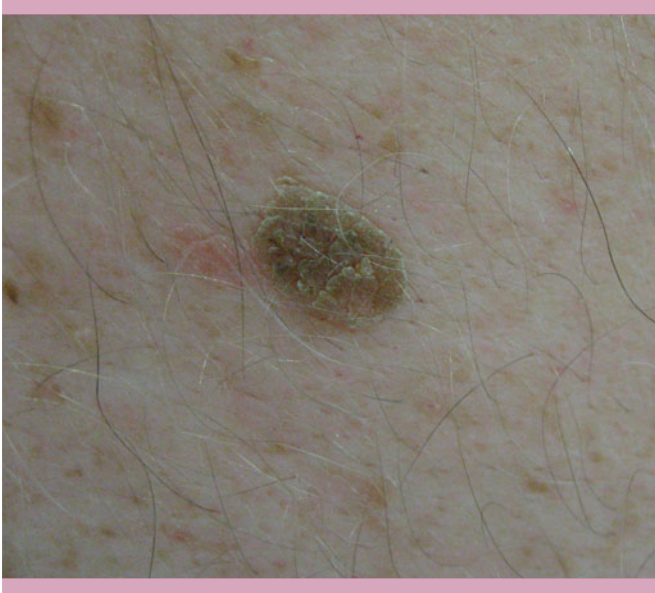


FIGURE 11-1 Seborrheic keratosis. (Courtesy of Dr. Asra Ali.)



FIGURE 11-2 Dermatitis papulosa nigra. (Courtesy of Dr. Asra Ali.)

- Nevus comedonicus: groups of open comedones on face, trunk, neck, and upper extremities that histologically show keratin-filled, epithelium-lined invaginations of the epidermis
- Nevus comedonicus syndrome: nevus comedonicus with abnormalities in the central nervous system (CNS), skeletal system, skin, and eye

Acrokeratosis Verruciformis of Hof

- Appearance: dry, rough, skin-colored verrucoid, keratotic papules



FIGURE 11-3 Epidermal nevus. (Courtesy of Dr. Asra Ali.)

- Location: dorsum of acral forearms, hands, and feet.
- Demographics: develops in infancy or early childhood
- Characterization: if multiple, can be associated with Darier disease
- Histology: hyperkeratosis, acanthosis, orthokeratosis, hypergranulosis, and mild papillomatosis with a “church spire” appearance

Intraepidermal Epithelioma of Borst-Jadassohn

- Characterization: currently regarded as a histopathological appearance rather than a precise clinicopathological entity
- Histology: nests of clonal keratinocytes in the background of a seborrheic keratosis, actinic keratosis, hidrocanthoma simplex, intraepidermal eccrine poroma, and Bowen disease

Porokeratosis (Fig. 11-4)

- Appearance: annular hyperkeratotic papule or plaque with atrophic center and peripheral grooved keratotic ridge
- Characterization: misnomer, no relationship to pore of eccrine duct



FIGURE 11-4 Porokeratosis. (Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)

- Histology: cornoid lamella (column of parakeratosis underlying hypogranulosis, corresponds to keratotic ridge clinically) in association with dyskeratotic cells
- Variations
 - Porokeratosis of Mibelli: usually presents in first decade; larger; plaque-like; more prominent cornoid lamella
 - Porokeratosis punctata palmaris et plantaris: begins in young adults; small foci, involves palms and soles
 - Linear porokeratosis: epidermal nevus affecting extremities; 1st decade; prominent cornoid lamellae histologically

Warty Dyskeratoma (Isolated Dyskeratosis Follicularis)

- Appearance: solitary, benign, hyperkeratotic, umbilicated lesion with keratotic plug
- Location: usually limited to the head, neck, or face (sun-exposed skin)
- Histology: epidermal cup-shaped invagination with focal acantholysis, dyskeratosis (corps ronds and grains), and overlying parakeratosis

Arsenical Keratosis

- Appearance: gray, hard, hyperkeratotic papules
- Location: usually on palms, forearms, soles, trunk, and face
- Characterization
 - Arsenic impairs nucleotide excision repair and enhances proliferation of human keratinocytes;



FIGURE 11-5 Mees lines. (Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)

- found in medications, Fowler solution, and well water
- Can turn into squamous cell carcinoma (most commonly) or basal cell carcinoma; also associated with internal malignancies (gastrointestinal tract adenocarcinoma)
- Mees lines on the fingernails (Fig. 11-5)
- Histology: thick, compact hyperkeratosis, parakeratosis, and acanthosis with atypical keratinocytes; may resemble Bowen's disease

Large Cell Acanthoma

- Appearance: solitary, slightly hyperkeratotic lesion with sharply demarcated borders, usually < 1 cm; occurs on sun-exposed areas
- Characterization: thought to represent at type of actinic keratosis, but now is considered by many to be a stage of solar lentigo evolution
- Histology: hyperkeratosis; keratinocytes are two times larger than normal without atypia; lentiginous hyperpigmentation

Clear Cell Acanthoma (Pale Cell Acanthoma)

- Appearance: solitary nodules and papules with well defined borders and covered with a crust, < 2 cm
- Location: usually on anterior surface of lower extremities
- Histology: proliferation of pale keratinocytes (periodic acid–Schiff (PAS) staining positive, due to cytoplasmic glycogen accumulation) with sharp demarcation from normal epidermis; neutrophils within the epidermis, often with microabscesses in stratum corneum and dilated capillaries in dermal papillae



FIGURE 11-6 Prurigo nodularis. (Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)

Epidermolytic Acanthoma

- Appearance: solitary tumor arising on the trunk of older patients
- Histology: compact hyperkeratosis, papillomatosis, acanthosis, perinucleolar vacuolization of keratinocytes in stratum spinosum, hypergranulosis with large basophilic keratohyaline granules and intracytoplasmic eosinophilic bodies (epidermolytic hyperkeratosis)

Prurigo Nodularis

- Appearance: multiple or solitary nodules, usually symmetric with excoriations present, extremely pruritic (Fig. 11-6)
- Characterization: part of the spectrum of lichen simplex
- Histology: psoriasiform hyperplasia, hyperkeratosis, hypergranulosis and focal parakeratosis, occasional spongiosis and exocytosis of mononuclear cells

Granuloma Fissuratum

- Appearance: firm, flesh-colored nodule with a central groove (site of focal pressure or friction)
- Location: lateral aspect of nose and retroauricular region
- Histology: acanthosis with broad rete ridges and central depressed area corresponding to the groove

CYSTS

Epidermoid Cyst (Epidermal Inclusion Cyst, Follicular Infundibular Cyst)

- Appearance: smooth dome-shaped swellings; punctum can be present (Fig. 11-7)



FIGURE 11-7 Epidermal inclusion cyst. (Courtesy of Dr. Asra Ali.)

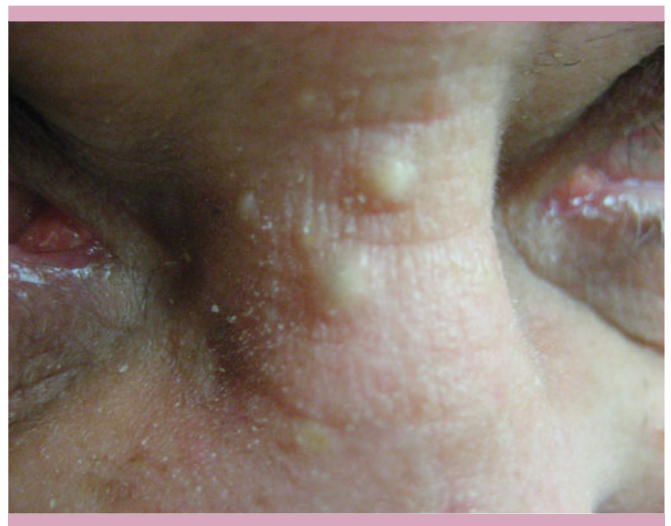


FIGURE 11-8 Milia. (Courtesy of Dr. Asra Ali.)

- Location: most often on face, neck, and trunk, but can occur anywhere
- Demographics: young and middle-aged adults
- Characterization: most common type of cyst of the skin
- Histology: cyst wall lined by squamous epithelium similar to surface epidermis with granular layer and containing lamellated keratin; cyst rupture can result in a prominent foreign body inflammatory reaction with foreign body giant cells, lymphocytes, plasma cells, and neutrophils
- Variations
 - Milium (plural: milia): Much smaller epidermoid cyst (1–2 mm) (Fig. 11-8)

Dermoid Cyst

- Appearance: subcutaneous freely mobile cyst; occasionally may fix to periosteum
- Location: most commonly found on the lateral upper eyelid, nose, and scalp; may have intracranial extension
- Demographics: develops in infancy or early childhood
- Characterization: hamartomatous lesion; due to sequestration of epithelium along embryonal lines of closure
- Histology: cyst wall lined by squamous epithelium with associated hair follicles and sebaceous glands and containing keratin and hair shafts

Pilar Cyst (Trichilemmal Cyst)

- Appearance: smooth, firm, mobile nodules
- Location: usually on scalp
- Characterization: derived from the outer root sheath of the hair follicle
- Histology: fibrous capsule lined by squamous epithelium lacking a granular layer with compact, dense keratin; calcification and cholesterol clefts common

Steatocystoma

- Appearance: moderately firm, translucent to yellow cystic nodules
- Location: commonly found in the axilla and on the arms, trunk, head, and neck.
- Characterization: true sebaceous cyst with epithelial lining that extrudes a yellowish oily material when punctured
- Steatocystoma simplex: solitary; adults
- Steatocystoma multiplex: autosomal dominant disorder (mutations in gene encoding keratin 17); adolescents
- Histology: dermal, folded cyst wall composed of keratinocytes with peripheral palisading basal cells; wall embedded with flattened lobules of sebaceous glands; cyst filled with eosinophilic cuticle along corrugated keratin layer; K17 and K10 staining positive

Hidrocystoma (Cystadenoma) (Fig. 11-9)

- Appearance: solitary, translucent, bluish cyst, 1–3 mm
- Location: most common on eyelid or cheek
- Histology: unilocular or multilocular intradermal cyst, lined by a double layer of cuboidal cells

Branchial Cleft Cyst

- Appearance: solitary, painless mass
- Location: lateral part of the neck; occurs along the lower third of the anteromedial border of the sternocleidomastoid muscle; 2–3 % of cases are bilateral
- Demographics: child or young adult
- Characterization: congenital epithelial cyst; remnant of the second branchial cleft in embryonic development

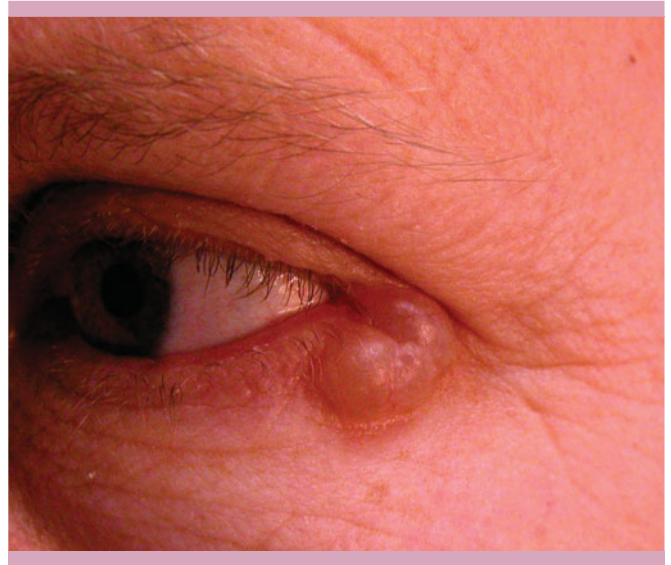


FIGURE 11-9 Hidrocystoma. (Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)

- Histology: lined by stratified squamous or respiratory (pseudostratified ciliated columnar) epithelium; lymphoid tissue often is present outside the epithelial lining

Thyroglossal Duct Cyst

- Appearance: solitary, fluctuant, painless mass; < 3 cm
- Location: midline neck, near hyoid bone; moves with swallowing
- Characterization: congenital, vestigial remnant of the tubular thyroid gland precursor
- Histology: lined by cuboidal, columnar, or stratified squamous ciliated epithelium associated with mucous glands, thyroid follicles, and lymphocytic infiltrate; smooth muscle is not present

Bronchogenic Cyst

- Appearance: small, solitary, painless mass
- Location: above sternal notch
- Demographics: present at birth
- Characterization: formed from portions of foregut during development of tracheobronchial tree
- Histology: intradermal, folded cyst lining; pseudostratified, cuboidal, or columnar ciliated epithelium with or without goblet cells, smooth muscle, or mucous glands

Vellus Hair Cyst

- Appearance: small solitary cysts, 1–2 mm
- Location: particularly over the parasternal area
- Histology: intradermal cyst lined by squamous epithelium (with granular layer) containing laminated

keratin and vellus hair shafts; K17 staining positive and K10 staining negative (in contrast to steatocystoma above)

- Variations:
 - Eruptive vellus hair cysts: multiple cysts on chest of children

DUCTAL (APOCRINE/ECCRINE) TUMORS

Apocrine/Eccrine Nevus

- Location: scalp, axilla, upper extremities, presternal, or inguinal area
- Characterization: rare hamartoma of apocrine or eccrine unit
 - Apocrine type usually located in axilla and lacks hyperhidrosis, while eccrine type usually has hyperhidrosis
- Histology: increased size or number of mature apocrine or eccrine glands

Eccrine Hamartoma

- Variations
 - Eccrine angiomatous hamartoma: increased number of eccrine glands with small blood vessels, nerve fibers, mucin, or fat
 - Porokeratotic eccrine ostial nevus: coranoid lamellae associated with eccrine ducts
 - Acrosyringal nevus: PAS-positive acrosyringal keratinocytes, which extends into the dermis as anastomosing cords
 - Linear eccrine nevus with comedones: similar to nevus comedonicus together with basaloid nests in the dermis

Tubular Apocrine Adenoma

- Appearance: rare, slow growing intradermal nodule; female predominance (2:1)
- Location: most often on scalp and perianal skin
- Histology: well-circumscribed dermal tumor (without epidermal connection) composed of well-formed tubules lined by a double layer of epithelium with abundant eosinophilic cytoplasm; luminal layer shows columnar cells with decapitation secretions, while the peripheral layer is composed of flattened or cuboidal myoepithelial cells

Nipple Adenoma (Erosive Adenomatosis, Florid Papillomatosis, Superficial Papillary Adenomatosis)

- Appearance: unilateral crusted papule or plaque
- Location: on the nipple; may mimic Paget disease
- Characterization: ductal hyperplasia of the lactiferous ducts

- Histology: mixture of intraductal papilloma and tubular glands with apocrine decapitation, lined by epithelial and myoepithelial cells, usually communicating with the surface epithelium; plasma or lymphocyte-rich inflammatory cell infiltrate sometimes in surrounding connective tissue

Hidradenoma Papilliferum

- Appearance: solitary, mobile nodule which may exhibit superficial erosion
- Location: vulva or perianal regions
- Demographics: young or middle-aged women
- Histology: well-circumscribed, cystic tumor (usually without communication with surface) with maze-like glandular spaces and epithelial covered papillary processes cover by two types of epithelium: tall columnar cells with decapitation secretions and peripheral flattened or cuboidal myoepithelial cell layer

Syringocystadenoma Papilliferum (Fig. 11-10)

- Appearance: erythematous, warty solitary plaque or linear arrangement of papules
- Location: most common on scalp
- Characterization: often found in association with nevus sebaceus (5–20%)
- Histology: epithelial-lined papillae invaginating from the overlying epidermis, lined with a double layer of cells (columnar layer with apocrine decapitation on the luminal side and a cuboidal layer at the periphery); fibrovascular cords with plasma cell-rich infiltrates

Cylindroma

- Appearance: pink, firm, rubbery nodules; solitary or multiple (turban tumors); arising sporadically or as part of the Brooke-Spiegler syndrome



FIGURE 11-10 Syringocystadenoma papilliferum. (Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)

- Location: most common on head, neck, and scalp
- Characterization: cylindroma and spiradenoma are considered a part of a spectrum of lesions; multiple cylindromas can occur in an autosomal dominant inherited mode; *CYLD1* gene, 16q12-q13; malignant cylindromas may develop
- Syndrome:
 - Brooke-Spiegler syndrome (BSS): autosomal dominant disease (*CYLD* gene on chromosome 9p21) characterized by the development of multiple trichoepitheliomas and cylindromas
- Histology: dermal tumor *without* connection to the overlying epidermis; multiple lobules of basaloid tumor cells, surrounded by a hyaline basement membrane and fit together like pieces of a jigsaw puzzle; eosinophilic hyaline sheaths and hyaline droplets are PAS staining positive (composed of type IV collagen and laminin)

Spiradenoma

- Appearance: solitary, painful intradermal nodule; sometimes multiple; sometimes with overlying blue skin; 1–2 cm; children and young adults
- Location: scalp, neck, and upper part of the trunk
- Histology: sharply demarcated dermal nodule; “big blue balls” in dermis under low-power view (no connection to epidermis) with connective tissue capsule; two cell types make up tumor lobules: peripheral dark small blue cells and central pale large blue cells; peripheral cells arranged in rosettes; can have overlapping features with cylindroma

Syringoma

- Appearance: usually multiple, skin-colored to tan, soft, pinpoint papules (Fig. 11-11)
- Location: lower eyelids and upper cheeks
- Demographics: commonly seen in females at puberty; associated with Down syndrome, Marfan syndrome, and Ehlers-Danlos syndrome
- Characterization: eccrine duct adenoma
- Histology: small ducts with elongated tails of epithelial cells (tadpole appearance) embedded in a sclerotic stroma; walls of the ducts usually lined by two rows of cuboidal epithelial cells; lumen filled with PAS staining positive eosinophilic, amorphous debris
 - Histologic differential diagnosis: sclerosing (morphea-like) basal cell carcinoma, desmoplastic trichoepithelioma, and microcystic adnexal carcinoma
- Variations
 - Eruptive syringomas: large crops on anterior chest, in children 4 to 10 years old, 18% of Down syndrome patients
 - Clear cell syringomas: associated with diabetes mellitus



FIGURE 11-11 Syringoma. (Courtesy of Dr. Melissa Bogle.)

Chondroid Syringoma (Mixed Tumor of the Skin)

- Appearance: solitary, skin-colored, slow growing firm nodule
- Location: head and neck
- Demographics: middle age, males more than females
- Histology: located in the dermis and subcutaneous tissue (no epidermal connection); multilobulated, clusters and solid cords of tumor cells together with ductal structures set in a chondroid, myxoid, and fibrous stroma; ductal structures are lined by two layers of cuboidal cells (resembling apocrine cells); areas of ossification (pseudocartilagenous appearance)

Eccrine Poroma

- Appearance: solitary, skin-colored, painless, firm to rubbery, dome-shaped nodule, < 2 cm in diameter
- Location: usually on scalp and sole of foot or palms
- Demographics: middle age
- Histology: solid masses of cuboidal or basaloid epithelial cells with ovoid nuclei; tumor in continuity with overlying epidermis; small sweat ducts with inner eosinophilic cuticle are usually present
- Variations
 - Eccrine poromatosis: greater than 100 papules on palms/soles
 - Intraepidermal poroma (hidroacanthoma simplex): nests of clonal basaloid cells with tubular differentiation; confined to the surface epidermis
 - Juxtaepidermal poroma: nests and thick cords of cells in continuity with the epidermis but also involving the superficial dermis

Eccrine Acrospiroma (Nodular Hidradenoma) (Fig. 11-12)

- Appearance: solitary, slow growing, painless intradermal nodule; usually < 2 cm in diameter
- Location: usually on scalp, face, or trunk
- Characterization: some authors consider hidroacanthoma simplex, poroma, dermal duct tumor, and hidradenoma under the unifying term of “eccrine acrospiroma”
- Histology: well circumscribed (not connected to epidermis) nests of tumor cells often in lower dermis



FIGURE 11-12 Eccrine acrospiroma. (Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)



FIGURE 11-13 Apocrine adenocarcinoma. (Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)

or subcutaneous tissue with two types of cells: fusiform, eosinophilic cells and polygonal, clear cells; sweat duct lumina present within tumor

- Variations
 - Clear cell hidradenoma: pale or clear cells containing glycogen (PAS staining positive)
 - Cystic nodular hidradenoma: common on scalp; prevalence of cysts (solid structures are present as well, as opposed to apocrine hidrocystoma)

Malignant Sweat Gland Tumors

- Appearance: solitary, slow growing papule or indistinct plaque
- Location: usually on upper lip, nasolabial area, or periorbital regions
- Characterization: infiltrating malignant tumor involving the dermis with ductal or glandular differentiation
- Histology: deeply infiltrating dermal strands of ductal cells with small lumina; pleomorphic, hyperchromatic, highly mitotic with areas of necrosis; perineural invasion common
- Variations
 - Primary mucinous carcinoma (cutaneous adenocystic carcinoma): slow growing, skin-colored, erythematous, or blue nodules or plaques; head and neck (especially eyelids); middle-age to elderly males (2:1); locally aggressive but rare metastasis
 - Histology: duct forming tumor cells suspended in abundant pools of mucin, compartmentalized by delicate fibrous septa
 - Adenoid cystic carcinoma: painful plaques; > 3 cm in diameter; middle-age to elderly women; affecting scalp, trunk and extremities
 - Histology: irregularly shaped, dermal aggregation of basaloid cells arranged in solid and/or sieve-like patterns (cribriform); the tumor nests are surrounded by hyaline basal-like material and cystic spaces contain mucin; propensity for perineural invasion; carcinoembryonal antigen (CEA) and EMA positive
- Microcystic adnexal carcinoma: indurated plaques or nodules on the upper lip, chin, nasolabial fold, cheek; aggressive local invasion and indolent course
 - Histology: desmoplastic stroma; keratinous cysts and abortive hair follicles in the superficial portion of the lesion and nests of basaloid cells (resembling sclerosing basal cell carcinoma) and small ducts lined by one or two layers of cuboidal cells (can have tail-like cellular extensions reminiscent of syringoma) in the deeper aspect of lesion; perineural invasion frequently seen; epithelial membrane antigen (EMA) and CEA staining positive
- Apocrine carcinoma (Fig. 11-13): rare, solitary or multiple nodules and plaques measuring 2 to 8 cm in diameter in the axillae or anogenital area
 - Histology: infiltrating dermal or subcutaneous nonencapsulated papillary tumor; ductal, solid, or mixed pattern; apocrine secretions and cords of neoplastic cells with variable pleomorphism; abnormal mitotic activity and necrosis; CAM 5.2, CEA, and S-100 protein immunoreactivity
- Malignant chondroid syringoma (malignant mixed tumor): extremely rare, solitary, painful, flesh-colored or erythematous nodule,

- predilection for trunk and distal extremities (foot most common)
 - Typically develops de novo, high metastatic rate (60%)
 - Histology: infiltrative growth pattern, abnormal mitoses, tumor necrosis
- Porocarcinoma: verrucoid plaque or polypoid growth; older individuals; usually on the lower extremities; metastasis about 20%
 - Histology: large islands and small, irregularly shaped nests with infiltrative borders; focal necrosis with clear cell areas, ductal structures, intracytoplasmic lumina formation, and squamous differentiation; PAS staining positive and usually diastase labile, cytokeratin, CEA, and EMA staining positive
- Spiradenocarcinoma: aggressive tumor, usually originates on a long-standing solitary lesion of spiradenoma on the lower extremities; local recurrences and metastasis
 - Histology: basaloid cells and occasional ductular differentiation that invade deep dermis and extend into the subcutaneous fat; focal areas of necrosis and mononuclear reactive inflammatory cell infiltration; low-molecular-weight cytokeratin and EMA staining positive

Paget's Disease (Mammary and Extramammary)

- Appearance: resembles non-resolving eczema, contact dermatitis, or Bowen's disease with intense pruritis
- Location: extramammary Paget's occurs in areas rich in apocrine sweat glands (groin, perianal, scrotum, or vulva)
- Characterization: association with internal malignancy
- Mammary Paget's: close to 100% intraductal breast cancer
- Extramammary Paget's: up to 15% underlying carcinoma (e.g., adnexal apocrine carcinoma, colonic carcinoma, etc.)
- Histology: Paget cells (large, vacuolated cells with a bluish cytoplasm) in the lower epidermis which spread along the rete ridges and adnexal (pagetoid spread); stain sialomucin with PAS and diastase, colloidal iron, and mucicarmine; Paget's cells are immunoreactive with EMA, CEA, cytokeratin 7
 - Immunostaining sometimes helpful for excluding associated internal malignancy

FOLLICULAR TUMORS

Trichoblastoma

- Appearance: well-circumscribed, solitary papule, < 1 cm

- Location: predominantly on the head and neck
- Histology: well-circumscribed dermal aggregates of epithelial, basaloid, and mesenchymal components in a fibromyxoid stroma that extend into the subcutaneous tissue; increased mitotic activity; minimal pleomorphism

Trichoepithelioma

- Appearance: dome-shaped papules
- Location: face, usually nasolabial folds
- Characterization: multiple lesions present as an autosomal dominant trait
- Syndromes
 - Brooke-Spiegler syndrome: multiple trichoepithelioma papules, particularly on the head and neck; also cylindromas in addition to spiradenomas and milia; increased risk of basal-cell adenomas and adenocarcinomas of the parotid glands and minor salivary glands; see cylindroma above
 - Rombo syndrome: vermiculate atrophoderma; milia; hypotrichosis; vellous hair cysts; basal cell carcinoma and peripheral vasodilatation with cyanosis
 - Bazex syndrome: follicular atrophoderma; hypotrichosis; basal cell carcinoma and localized or generalized hypohidrosis
- Histology: palisading basaloid cells in a dense stroma; horn cysts with keratinized center; calcification; papillary mesenchymal bodies; artifactual clefting is uncommon (in contrast from basal cell carcinoma); lack of deep and infiltrating growth pattern, perineural infiltration, and ductal differentiation (in contrast from microcystic adnexal carcinoma)
- Variations
 - Desmoplastic trichoepithelioma: prominent sclerotic stroma, narrow strands of tumor cells, and keratinous cysts with calcification (resembling sclerosing basal cell carcinoma); pleomorphism, palisading, and peripheral clefting are not seen; particularly important to exclude microcystic adnexal carcinoma
 - Solitary giant trichoepithelioma: deep involvement of the reticular dermis and subcutaneous tissue
 - Trichoadenoma: rare solitary tumor located on the face, up to 5 cm in size; groups of horn cysts connected by epithelial strands; cells more squamous than basaloid

Trichofolliculoma

- Appearance: small, solitary, elevated papule, or flattened nodule with central depression and protruding tuft of small, short, white, or pigmented thread-like hairs (trichoids)

- Location: face
- Histology: cystic tumor lined by squamous epithelium (usually communicating with the surface); fully formed vellus units within cyst wall; radiating secondary follicular buds that project into the surrounding dermis
- Variations
 - Sebaceous trichofolliculoma: small sebaceous elements found within the follicular units
 - Pilar sheath acanthoma: usually on the upper lip of adults; keratin-filled dilated follicular infundibulum; marked lobular epithelial proliferation composed of outer root sheath squamous epithelium; without hair shafts, but vellus hairs can be seen in the wall of the cyst
 - Dilated pore of Winer: usually on the face or trunk; dilated open follicular cystic cavity filled with keratin and irregular budding of the epithelium on the lateral aspect of the pore

Fibrofolliculoma

- Appearance: multiple small dome-shaped papules
- Location: face, neck, and upper trunk
- Syndrome
 - Birt-Hogg-Dube syndrome: Autosomal dominant (BHD gene on 17p11.2); association of fibrofolliculomas, acrochordons, trichodiscomas and pulmonary disease (spontaneous pneumothorax); renal tumors
- Histology: cystically dilated, well-formed hair follicle with a central keratin plug and anastomosing strands of basaloid cells arising from the infundibulum; surrounded by a fibrous stroma; residual sebaceous glands are often incorporated into the lesion

Trichodiscoma

- Appearance: small dome-shaped papules
- Location: face, neck, and upper trunk
- Characterization: proliferation of the hair mantle
 - Fibrofolliculoma and trichodiscoma may represent various stages in the natural history of a single hamartomatous tumor
- Histology: horizontally oriented proliferation of epithelial cords surrounded by prominent stroma that contains fusiform and stellate fibroblasts and thin-walled blood vessels within the substance of the tumor

Trichilemmoma (Tricholemmoma)

- Appearance: single papule or multiple, small, flesh-colored papules or warty lesions
- Syndrome
 - Cowden syndrome: autosomal dominant; multiple facial trichilemmomas, acral keratoses, dermal fibromas, oral mucosal papillomas, and

systemic malignancies (e.g., thyroid, breast, and endometrial carcinomas); dysfunctional lipid phosphatase enzyme secondary to loss of *PTEN* (10q23)

- Histology: endophytic epithelial lobule with peripheral basal cell palisading; thickened eosinophilic hyaline basement membrane zone; cells located toward the center are clear (increased glycogen, PAS staining positive)
- Variations
 - Desmoplastic tricholemmoma: lobulated tumor that has at the base narrow, irregular cords that infiltrate into the dermis; infiltrating pattern commonly mistaken for malignant tumor (e.g., trichilemmal carcinoma, squamous cell carcinoma, or morpheaform basal cell carcinoma)
 - Tumor of the follicular infundibulum: solitary keratotic papule on the face; dermal growth of clear epithelial cells parallel to the epidermis; peripheral palisading of the basal cells

Pilomatricoma (Calcifying Epithelioma of Malherbe)

- Appearance: solitary, firm, deep-seated dermal or subcutaneous nodule
- Perforation with extrusion of contents; “tent sign” elevates skin (clinically mistaken for a cyst)
- Location: predilection for the head, shoulders, and upper extremities
- Demographics: occurs at any age; most common in children and young adults
- Characterization: activating point mutation in *CTNNB1* with accumulation of nuclear beta-catenin
- Histology: irregularly shaped islands embedded in cellular stroma; composed of two cell types: small uniform basaloid cells with high mitotic activity (early lesion) and necrotic cells with eosinophilic cytoplasm and lost nucleus (shadow cells, older lesion); transitional areas where basal cells turn into shadow cells; calcification, ossification, keratin debris predominant in older lesions with foreign body giant cell reaction; pilomatrical features can rarely be seen in the epidermoid inclusion cysts and is believed to be pathognomic of Gardner syndrome

Proliferating Trichilemmal Cyst (Pilar Tumor)

- Appearance: rare, large dermal nodule
- Location: most common on scalp
- Characterization: arises as proliferating wall of pilar cyst with abrupt trichilemmal keratinization
- Histology: well-circumscribed nodule with trichilemmal keratinization (without granular layer); horn pearls and squamous eddies

SEBACEOUS TUMORS

Sebaceous Hyperplasia

- Appearance: white-yellow, well-demarcated, small papules with central umbilication (Fig. 11-14)
- Location: face, especially forehead and nose
- Histology: increased number of enlarged sebaceous lobules grouped around a centrally located, wide sebaceous duct

Sebaceous Adenoma

- Appearance: solitary, yellow papule or nodule; < 1 cm
- Location: usually on the face or scalp
- Demographics: middle-aged adults
- Syndrome
 - Muir-Torre syndrome: autosomal dominant, defect in DNA mismatch repair (MMR) gene with loss of hMSH2 or (less commonly) hMLH1 protein expression; one or more sebaceous neoplasms (sebaceous adenoma, sebaceoma, or rarely sebaceous carcinoma) and one or more visceral malignancies (most commonly gastrointestinal, endometrial or genitourinary carcinomas)
- Histology: well-circumscribed multilobulated neoplasm composed of mature sebaceous cells (sebocytes) representing up to 50% of the tumor and peripheral, smaller basaloid (germinative) cells

Sebaceoma

- Appearance: solitary, yellow ill-defined plaque, 1–3 cm in diameter
- Location: face and scalp
- Demographics: 6th–9th decade; female predominance (4:1)
- Syndrome:
 - Muir-Torre syndrome: see Sebaceous Adenoma above
- Histology: composed of sebocytes and smaller basaloid (germinative) cells that represent more than 50% of the total lesional cells

Nevus Sebaceus of Jadassohn (Fig. 11-15)

- Appearance: three clinical stages
 - At birth: solitary, hairless, pinkish, yellow, orange, or tan plaque with a smooth or somewhat velvety macular surface
 - Puberty: lesion becomes verrucous and nodular; sebaceous glands enlarge and cause papillomatosis
 - Later in life: lesions may develop various types of appendageal tumors including: syringocystadenoma papilliferum (8–10%), trichoblastoma (5%), and rarely trichilemmoma (2–3%), sebaceoma (2–3%), syringoma, apocrine cystadenoma, hidradenoma or keratoacanthoma



FIGURE 11-14 Sebaceous hyperplasia. (Courtesy of Dr. Asra Ali.)



FIGURE 11-15 Nevus sebaceus. (Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)

- Apparently benign basaloid epithelial proliferations resembling basal cell carcinoma can be identified in 5–7% of cases of nevus sebaceus
- Malignant tumors (apocrine carcinoma, basal cell carcinoma, squamous cell carcinoma) have been described to arise in association with nevus sebaceus on occasion
- Location: face or scalp
- Syndrome
 - Neurocutaneous syndrome: mental retardation; epilepsy; neurologic deficits; skeletal deformities (rare)
 - Epidermal nevus syndrome (Schimmelpenning-Feuerstein-Mims syndrome, organoid nevus phakomatosis): combination of extensive sebaceous nevi with central nervous system, cardiac, ophthalmic, and skeletal muscle disorders
- Histology: papillomatous and acanthotic hyperplasia; numbers of mature or nearly mature sebaceous glands are increased in the dermis; ectopic apocrine glands in the deep dermis beneath sebaceous glands; reduced number of hair follicles, incompletely differentiated

Sebaceous Carcinoma

- Appearance: firm, slow growing, yellowish nodule
- Location: 75% arise in the periocular region: upper lid two to three times more common than lower lid, often mistaken for a chalazion; can mimic keratoconjunctivitis, blepharoconjunctivitis
- Demographics: 6th–7th decade
- Characterization: aggressive clinical course with high recurrence rate (up to 40%); metastasis occurs in 14–25% of cases, first to the draining lymph nodes with progression to distal or visceral metastases
- Syndrome
 - Muir-Torre syndrome: non-periocular sebaceous carcinomas are much more commonly associated with the syndrome; see Sebaceous Adenoma
- Histology: infiltration of dermis by lobules composed of a mixture of small basaloid (germinative) cells and poorly differentiated sebaceous cells; marked pleomorphism and frequent abnormal mitoses, necrosis common; pagetoid spread is seen in 40–80% of cases; oil red-O staining can be performed in frozen sections to highlight the sebocytes

FIBROUS AND “FIBROHISTIOCYTIC” TUMORS

Fibroma

- Appearance: pale brown, soft, small tumors in friction areas: neck, axilla, internal aspects of thighs

- Histology: tumors are formed by connective tissue; fibrocytes are regular and mature; mitoses are not present

Angiofibroma (Fibrous Papule)

- Appearance: small, reddish-brown papules
- Location: usually over the nose and medial cheeks
- Syndrome
 - Tuberous sclerosis: autosomal dominant, genetic linkage to chromosome 9q34 (*TSC1*) or 16p31 (*TSC2*) in families with tuberous sclerosis; two-thirds of cases are sporadic and majority appear to be related to new mutations of *TSC2*; multiple, bilateral angiofibromas near the nasal labial folds at puberty (adenoma sebaceum); periungual fibromas; white macular lesions (shagreen patches), enamel teeth pits; central nervous system involvement (epilepsy and low intelligence); ophthalmological, cardiac, and pulmonary manifestations, among others
 - Multiple endocrine neoplasia type I: familial tumor syndrome with facial angiofibromas, collagenomas, lipomas, gastrinomas, insulinomas, prolactinomas, and carcinoid tumors.
- Histology: concentrically oriented (around follicles) or perpendicular (to the epidermis) laid collagen fibers with stellate fibroblasts; teleangiectasia
- Variations
 - Pearly penile papules: angiofibromas in penile coronal sulcus

Dermatofibroma (DF), (Benign Fibrous Histiocytoma) (Fig. 11-16)

- Appearance: usually firm, solitary, pink, brown, yellowish nodule, sometimes polypoid; dimples with pressure
- Location: often on the extremities
- Histology: fibrohistiocytic proliferation entrapping eosinophilic bundles of collagen at the periphery of the lesion; foamy histiocytes, multinucleated giant cells, and vessels in variable proportion are also seen; the overlying epidermis is acantholytic with tabled rete ridges and increased pigmentation of basal keratinocytes (induction phenomenon)
- Variations
 - Cellular dermatofibroma: larger with higher recurrence rate, more cellular with greater number of fibroblasts, can infiltrate fat and resemble dermatofibrosarcoma protuberans
 - Aneurysmal (hemosiderotic) dermatofibroma: large dilated blood spaces without endothelial lining; extravasated red blood cells with associated hemosiderin deposition; commonly mistaken for a vascular tumor



FIGURE 11-16 A. Cellular dermatofibroma. B. Dermatofibroma and dimple sign. (Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)

- Atypical dermatofibroma (Dermatofibroma with giant cells): large, atypical giant cells with pleomorphic nuclei and prominent nucleoli
- Atrophic dermatofibroma: hypocellular with atrophic epidermis and hyalinization of collagen
- Xanthomatous dermatofibroma: foamy macrophages that resemble a xanthoma, Touton giant cells sometimes



FIGURE 11-17 Hypertrophic scar. (Courtesy of Dr. Asra Ali.)

- Palisading dermatofibroma: prominent nuclear palisading; verocay-like bodies; can resemble Schwannoma
- Epithelioid cell histiocytoma: exophytic nodule or polypoid tumor with epidermal collarette, clinically resembling pyogenic granuloma or intradermal Spitz nevus; composed of epithelioid cells with abundant cytoplasm, numerous giant cells, and foamy macrophages
- Sclerotic fibroma: hypocellular with well circumscribed hyalinized plywood pattern of dense collagen
- Dermatomyofibroma: shoulder of younger women, bundles of spindle cells parallel to epidermis, can resemble leiomyoma or dermatofibrosarcoma protuberans; actin staining positive and CD34 staining negative; may be a distinct entity rather than BFH variant

Scar

- Characterization: due to dermal and/or subcutaneous traumatic or iatrogenic tissue damage
- Histology: bands of fibroblasts and dense collagen, often oriented parallel to the epidermis; granulation tissue present early with progression to collagen deposition and fibrosis
- Variations
 - Hypertrophic scar: thick, elevated scar that does not extend beyond the boundaries of the initiating injury; most frequently on the head and neck, shoulders, chest, and knees; no racial predilection (Fig. 11-17)
 - Keloid (Fig. 11-18): same as hypertrophic scar but extends beyond the boundaries of the initiating injury; more common on head and



FIGURE 11-18 Keloid. (Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)

neck (especially ear) and chest; more frequent in African descent; thick hyalinized bundles of eosinophilic collagen, less cellular than hypertrophic scar

Fibromatosis

- Demographics: present at birth or developing later in life.
- Characterization: group of benign soft tissue tumors characterized by proliferation of mature fibroblasts and collagen with infiltrative growth pattern, and potential local recurrence
- Histology: whorls of spindle cells; no mitosis
- Variations
 - Infantile myofibromatosis: multiple, solitary, rubbery slow growing nodules at birth; whorls of spindle cells with no mitoses; if multiple, associated with visceral involvement (35% cases); surgical excision with spontaneous remission and scarring
 - Congenital generalized fibromatosis: multiple, one to hundreds of nodules; bone can be involved
 - Infantile digital fibromatosis (inclusion body fibromatosis, Reye tumor): small (< 1cm), rapidly growing dermal or subcutaneous nodule(s), on dorsolateral digits; surgical excision with spontaneous remission, but local recurrence common (up to 50%)
 - Histology: eosinophilic intracytoplasmic inclusion bodies (smooth muscle actin staining positive, Masson-trichrome positive).
 - Juvenile hyaline fibromatosis: autosomal recessive; slow growing, skin-colored papules and nodules; often on the face, scalp, and back;

preceded by flexural contractures and gingival hyperplasia

- Genetics: mutations of 4q21 which encodes capillary morphogenesis protein 2 (CMG2)
- Histology: irregular, poorly circumscribed masses of deeply eosinophilic, hyalinized, collagen-like material (PAS staining positive, EM: microfilaments) and spindle fibroblasts
- Palmar and plantar fibromatosis (Dupuytren's contracture and Ledderhose disease): firm nodules in the distal palmar aponeurosis with progression to crippling flexion at the metacarpophalangeal joints (4th and 5th digits); questionable association with alcoholism
- Penile fibromatosis (Peyronie's disease): solitary or multiple fibrous plaques adjacent to the corpora cavernosa, causing curvature of the dorsal surface of the shaft; middle aged to adult males
- Knuckle pads: hyperkeratosis of the dorsal aspect of the joints of the fingers, without significant symptoms or contracture
- Desmoid fibromatosis: deeper fibromatosis usually only secondarily involving dermis; associated with activating mutations in *CTNNB1*, the gene encoding β -catenin; a variant is associated with Gardner syndrome (Gardner fibroma)

Angiomatoid Fibrous Histiocytoma

- Appearance: slow growing, painless subcutaneous nodule
- Location: extremities or trunk
- Demographics: children or young adults of either sex
- Characterization: sometimes present with systemic symptoms including fever, weight loss, anemia, and paraproteinemia; *FUS-ATF1*, *EWSR1-CREB1*, and *EWSR1-ATF1* (most frequent genetic alteration in clear cell sarcoma) have been detected in the few cases published, pointing to the interchangeable role of *FUS* with *EWSR1* and *ATF1* with *CREB1*
- Histology: relatively uniform, pale, round or short spindle-shaped eosinophilic cells with ovoid vesicular nuclei, interspersed with blood-filled sinusoidal spaces and foci of hemorrhage; desmin, muscle actin (HHF-35), CD99, and CD68 immunoreactive (up to 50% of cases), smooth muscle actin is negative

Giant Cell Tumor of the Tendon Sheath (Fig. 11-19)

- Appearance: slow growing, painless nodules fixed to a tendon sheath or fascia
- Location: dorsal aspect of the hand
- Demographics: 3rd-5th decade, slightly female predominance



FIGURE 11-19 Giant cell tumor of tendon sheath. (Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)

- Histology: proliferation of fibroblasts and foamy histiocytes, multinucleated giant cells (osteoclast-like), and areas of hemorrhage and hemosiderin deposition

Atypical Fibroxanthoma (AFX)

- Appearance: locally aggressive, red plaque or nodule of sun exposed skin
- Location: located on the head (especially ear), neck, and dorsa of the hands
- Demographics: elderly
- Characterization: rarely metastasize
- Histology: proliferation of bizarre spindle-shaped, foamy, and pleomorphic cells in the background of dermal solar elastosis; sometimes giant cells; many atypical mitosis; CD68 and CD10 staining positive, S100 and cytokeratin staining negative

Malignant Fibrous Histiocytoma (MFH)

- Appearance: deep subcutaneous mass
- Location: extremities (especially lower);
- Demographics: most common soft tissue sarcoma occurring in late adult life; male predominance (2:1)
- Histology: proliferation of fibroblasts, histiocyte-like cells, and bizarre giant cells with severe pleomorphism; may show atypical mitosis
- Variations
 - Storiform/pleomorphic: most common.
 - Myxoid MFH (myxofibrosarcoma): myxomatous stroma; curvilinear thin-walled blood vessels; hyperchromatic stellate or spindle-shaped cells



FIGURE 11-20 Dermatofibrosarcoma protuberans. (Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)

- Inflammatory MFH: usually in deep soft tissue; bland or atypical xanthomatous cells, neutrophils, and giant cells
- Giant cell MFH: osteoclast-like giant cells

Dermatofibrosarcoma Protuberans (DFSP) (Fig. 11-20)

- Appearance: slow growing plaque that often progresses to a multinodular mass
- Location: trunk or extremities
- Demographics: 3rd–4th decade
- Characterization: rare metastasis with local recurrences; ring chromosomes derived from chromosome 22 (adults) and t(17;22) are the most frequent finding, leading to fusion of *COL1A1* and *PDGFB* with strong overexpression of PDGFβ (platelet-derived growth factor)
- Histology: spindle, monomorphous cells; often storiform growth pattern with infiltration in honeycomb-like arrangement into the subcutaneous adipose tissue; myxomatous areas and polymorphous cells may be present; few mitosis; CD34 immunoreactive; S-100 protein and Factor XIIIa staining negative
- Variations
 - Bednar tumor (pigmented DFSP): prominent deposits of melanin and dendritic melanocytes;
 - Fibrosarcomatous DFSP: more cellularity, atypia, and mitosis; focal fascicular or “herring-bone”

pattern; represents transformation to a higher grade tumor with up to 20% metastatic rate

- Myxoid DFSP: extensive myxoid degeneration
- Giant cell fibroblastoma: occurs in children on the chest wall, back, thighs; previously separate, but now with same chromosomal abnormalities as DFSP, t(17;22)
 - Histology: variable myxoid, sclerotic, and sometimes dermatofibrosarcoma-like areas; cleft-like, angiomatoid pseudovascular spaces with scattered multinucleated giant cells

SMOOTH MUSCLE TUMORS

Congenital Smooth Muscle Hamartoma

- Appearance: solitary patch with or without a follicular pattern; diffuse skin involvement produces a “Michelin-tire baby” appearance; vellus hairs prominent
 - *Vermiculation*: wormlike movements upon stroking the lesion.
 - *Pseudo-Darier’s sign*: stroking induces transient induration with piloerection
- Location: trunk
- Histology: marked increase of smooth muscle fibers in the dermis; grouped fibers are in bundles arranged haphazardly and are not attached to hair follicles; basal hyperpigmentation

Leiomyoma

- Appearance: small, firm, pink solitary or multiple nodules; often painful
- Location: limbs or trunk
- Demographics: young adults
- Histology: fascicles of smooth muscle with blunt borders; fusiform cells with longitudinal striations and thin, cigar-shaped nuclei with blunt ends; desmin and smooth muscle actin staining positive, Verhoeff-van Gieson staining positive (yellow), trichrome staining positive (pink-red)
- Variations
 - Piloleiomyoma: arise from arrector pili muscle, infiltrative pattern
 - Dartotic leiomyoma: arise from the scrotal dartos muscle
 - Angioleiomyoma: benign deep dermal or subcutaneous nodule, well-circumscribed, arising from vascular smooth muscle; most common on lower leg
 - Histology: numerous thick walled blood vessels with a thick wall surrounded by bundles of smooth muscle
 - Angiomyolipoma: adipose tissue present with smooth muscle and vessels in variable degree

Leiomyosarcoma

- Appearance: pink dermal or subcutaneous nodule
- Location: common on extremities
- Demographics: peak in 5th-6th decade
- Characterization: malignant tumor of smooth muscle; negligible metastatic rate if confined to dermis, high metastatic rate if found deeper
- Histology: high cellularity with pleomorphic and hyperchromatic spindle cells; high mitotic activity; occasional necrosis; desmin and smooth muscle actin immunoreactive

ADIPOSE TISSUE TUMORS

Lipoma (Fig. 11-21)

- Appearance: solitary or multiple elastic nodules of the subcutis
- Location: usually on the arms, shoulders, back, lower extremities
- Characterization: benign tumor of the mature fat
- Histology: well-circumscribed proliferation of mature fat; fine capsule sometimes
- Variations
 - Angiolipoma: usually seen in young adults as subcutaneous lesions, sometimes painful; many small blood vessels, often thrombi
 - Fibrolipoma: intermixed fibrous tissue
 - Myolipoma: smooth muscle actin and desmin staining positive
 - Infiltrating lipoma: skeletal muscle between adipocytes



FIGURE 11-21 Lipoma. (Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)

- Spindle cell lipoma: posterior neck or upper back; spindle cells resembling fibroblasts admixed with thick, “ropey” collagen; CD34 staining positive
- Pleomorphic lipoma: posterior neck; atypical hyperchromatic multi-nucleated giant cells, with nuclei arranged in a floret pattern (floret giant cells); may resemble liposarcoma
- Adiposis dolorosa (Dercum disease): multiple painful, circumscribed lipomas; buttocks, lower limbs, and abdomen; post-menopausal women
- Hibernoma: upper back, axilla, chest wall, thigh; young adults; fetal adipocytes (brown fat) with central nucleus and multiple small vacuolated and granular cytoplasm, often lobulated and divided by fine fibrous septa
- Multiple symmetric lipomatosis: symmetrical involvement of trunk or proximal limbs in male children or cervical region involvement in middle-aged males (Madelung disease)

Liposarcoma

- Appearance: malignant tumor of soft tissues with rapid growth, usually larger than lipomas
- Location: deep soft tissue (retroperitoneum, thigh and buttock)
- Demographics: > 5th decade
- Histology: lipoblasts with cytoplasmic lipid-laden vacuoles; causes indentation of the hyperchromatic nucleus; variable nuclear polymorphism
- Variations
 - Well-differentiated liposarcoma: can be lipoma-like with occasional lipoblasts and scattered atypical cells with hyperchromatic nuclei; sometimes history of large recurrent lipoma
 - Dedifferentiated liposarcoma: areas of well differentiated liposarcoma with adjacent nonlipogenic (dedifferentiated) component, usually with abrupt interface; dedifferentiated zones have appearance of high grade sarcoma or malignant fibrous histiocytoma
 - Myxoid liposarcoma: spindle cells in a mucinous stroma and prominent vascular pattern (branched “chicken wire” capillaries); associated with t(12;16) fusing *DDIT3* and *FUS*
 - Round cell liposarcoma: more cellular with dense, small round hyperchromatic nuclei (variant of myxoid liposarcoma that is more aggressive, but with same translocation)
 - Pleomorphic liposarcoma: highly pleomorphic spindle cells and bizarre multinucleated multi-vacuolated giant cells; increased mitosis

Lipoblastoma

- Appearance: slow growing subcutaneous mass
- Location: extremities, head and neck, trunk

- Demographics: infancy and childhood (< 3 yrs age)
- Histology: lipoblasts, mature adipocytes, and pre-lipoblasts in a lobular pattern and separated by a loose fibrous septa; can resemble well-differentiated liposarcoma but found in young children

Nevus Lipomatosus Superficialis

- Appearance: multiple soft, yellow to skin colored papules and nodules
- Location: hip or buttock
- Demographics: newborn or infant
- Histology: lobules of mature adipose tissue in the superficial dermis

NEURAL TUMORS

Neuroma

- Appearance: skin-colored papules or nodules, often painful
- Syndrome
 - Multiple mucosal neuroma syndrome (multiple endocrine neoplasm, MEN type IIb or III): autosomal dominant; multiple mucosal neuromas (e.g., lip, tongue, and eyelid); pheochromocytoma and medullary carcinoma of the thyroid
- Histology: normal appearing or hyperplastic nerve bundles surrounded by fibrotic stroma; S-100 protein and myelin basic protein staining positive
- Variations
 - Traumatic neuroma (amputation neuroma): sites of trauma (e.g., scars)
 - Palisaded encapsulated neuroma (PEN): solitary; found on face (e.g., nose, nasolabial folds, and cheeks) of adults; usually well-circumscribed, but not truly encapsulated; palisading not as common as name implies
 - Morton neuroma: not a true neuroma, but represents a degenerative response to chronic low-grade tissue damage; usually found between the toes

Neurofibroma

- Appearance: solitary, soft papules or polypoid nodules
- Syndrome
 - Neurofibromatosis type I (NF-1, von Recklinghausen disease, peripheral neurofibromatosis): autosomal dominant, mutation of a gene on chromosome 17q (defect in neurofibromin protein, a negative regulator of the Ras oncogene); café-au-lait macules; freckling of axilla or groin (Crowe sign); optic gliomas, iris hamartomas, and distinctive osseous lesions (e.g., sphenoid dysplasia and thinning of long bone cortex)

- Neurofibromatosis type II (NF-2, multiple inherited schwannomas, meningiomas, and ependymomas—MISME—syndrome): autosomal dominant, mutation of a gene on chromosome 22 band q11–13.1 (defect in Merlin, tumor suppressor protein); bilateral cranial nerve (CN) VIII masses; multiple schwannomas (e.g., vestibulocochlear schwannomas), meningiomas, gliomas, and ependymomas; juvenile posterior subcapsular lenticular opacity (juvenile cortical cataract)
- Histology: fusiform, fine, often wavy spindle cells and fine collagenous fibers; sometimes compact, loose or even myxoid; S-100 protein staining positive
- Variations
 - Plexiform neurofibroma: involves an entire large nerve with its branches (“bag of worms” on palpation); can be associated with soft tissue overgrowth; pathognomonic of neurofibromatosis 1 (NF-1)
 - Diffuse neurofibroma: occurs on head, neck, and trunk; primarily children and young adults; plaque-like elevation of skin with ill-defined area of subcutaneous thickening; infiltrating neurofibromatous tissue with uniform, delicate collagenous stroma; 20–30% of cases associated with NF-1

Schwannoma (Neurilemmoma)

- Appearance: benign, solitary or multiple, small papules or nodules, sometimes painful
- Histology: encapsulated subcutaneous nodule; proliferation of Schwann cells with elongated nuclei and blunted ends; two often intermixed histologic patterns (Antoni A and B)
 - Antoni A: cells form loose fascicles with nuclei aligned in parallel arrays (Verocay bodies); S-100 protein positive
 - Antoni B: less cellular areas; myxoid and edematous

Dermal Nerve Sheath Myxoma (Neurothekeoma)

- Appearance: solitary, raised soft papules and nodules, < 3 cm in diameter
- Location: usually on the face or upper extremities
- Histology: well-defined, lobulated dermal mass with lobules of spindle and epithelioid cells in myxoid matrix, separated by thin fibrous septa; sparse mitotic activity; S-100 protein positive

Granular Cell Tumor

- Appearance: small papules and nodules
- Location: can occur anywhere, but frequent on oral mucosa (especially tongue), trunk or extremities (especially arms)

- Demographics: 3rd–6th decade
- Histology: round cells with brightly eosinophilic, granular cytoplasm (pustule-ovoid bodies of Milian; phagolysosomes; PAS staining positive); pseudoepitheliomatous hyperplasia; S-100 protein positive

OTHER TUMORS

Acquired Digital Fibrokeratoma (Fig. 11-22)

- Appearance: slow growing, firm nodule or outgrowth from a digit or acral skin
- Histology: pedunculated papule with hyperkeratosis and acanthosis; mature fibroblasts, small blood vessels, and elastic tissue in the dermis; dense dermal collagen fibers oriented parallel to the long axis of the lesion

Osteoma Cutis (Cutaneous Ossification)

- Appearance: dermal or subcutaneous white papule or nodule
- Syndrome
 - Albright’s hereditary osteodystrophy: short stature, obesity, round face, mental weakness, and cutaneous ossifications of the dermis and fat; characterized by a lack of renal responsiveness to parathyroid hormone
- Histology: spicules of bone in the dermis or subcutaneous tissue with cement lines, osteocytes, osteoblasts, and multinucleated osteoclasts

Supernumerary Digit

- Appearance: skin-colored outgrowth
- Location: hands, feet; usually near the fifth finger



FIGURE 11-22 Acquired digital fibrokeratoma. (Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)



FIGURE 11-23 Acrochordon. (Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)

- Demographics: congenital
- Histology: dome-shaped, fibrous stroma with many nerves and sometimes cartilage or bone

Acrochordon (Skin Tags, Fibroepithelial Polyp)

- Appearance: solitary or multiple, skin-colored papules (Fig. 11-23)
- Location: neck, axilla, inguinal areas, and eyelids
- Histology: pedunculated polyps covered by epidermis; papillomatosis and acanthosis; fibrovascular stroma with fat tissue and dilated blood vessels
- Variations
 - Lipofibroma: acrochordon with large percentage of fat cells

Accessory Tragus (Fig. 11-24)

- Appearance: asymptomatic congenital structure
- Location: preauricular area or neck



FIGURE 11-24 Accessory tragus. (Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)

- Histology: pedunculated papule or nodule with connective tissue, fat, and sometimes cartilage; many vellus hair follicles

Accessory Nipple (Supernumerary Nipple)

- Appearance: small congenital pigmented or skin-colored macule or concave/umbilicated papule (Fig. 11-25)
- Location: embryonic milk line
- Histology: identical to that of the regular nipple; epidermis present over central pilosebaceous structure, and dermis containing smooth muscle bundles and mammary glands/ducts

Merkel Cell Carcinoma (Neuroendocrine Carcinoma of the Skin, Trabecular Carcinoma)

- Appearance: rapidly growing nodules
- Location: sun-damaged skin (e.g., head and neck)
- Demographics: elderly
- Characterization: aggressive tumor with high metastatic potential
- Histology: strands or trabeculae, as well as nests, of undifferentiated tumor cells with scant cytoplasm, round to oval nuclei with fine chromatin,



FIGURE 11-25 Accessory nipple. (Courtesy of the Department of Dermatology, University of Texas Medical Branch at Galveston.)

and inconspicuous nucleolus (histologically similar to small cell carcinoma of the lung); CK20 and Cam 5.2 staining positive (paranuclear dot-like pattern); NSE, synaptophysin, and chromogranin staining positive; S-100 protein, carcinoembryonic antigen (CEA), and leukocyte common antigen (LCA) staining negative

Cellular Neurothekeoma

- Appearance: dermal nodule
- Location: head, neck, and upper trunk
- Demographics: children and young adults
- Histology: consists of nests and fascicles of epithelioid and spindle cells; S-100 protein staining negative, but reactive for NKI-C3

Primitive Non-Neural Granular Cell Tumor

- Appearance: exophytic, polypoid papule to nodule
- Location: variety of sites
- Demographics: wide age range
- Histology: this rare tumor consists of oval to spindle-shaped cells with prominent granular cytoplasm; CD68 staining focally positive, NKI-C3 (non-specific marker of lysosomes) staining diffusely positive, S-100 protein staining negative and is thus probably unrelated to the classic granular cell tumor described above

QUIZ

Questions

1. A patient with multiple trichilemmomas is at increased risk of which of the following malignancies?
 - A. Oral squamous cell carcinoma
 - B. Microcystic adnexal carcinoma
 - C. Basal cell carcinoma
 - D. Breast carcinoma
 - E. Malignant chondroid syringoma
2. An 8-year-old girl presents with multiple syringomas on her anterior chest. What syndrome is this entity most commonly found?
 - A. Birt-Hogg-Dube syndrome
 - B. Brooke-Spiegler syndrome
 - C. Down syndrome
 - D. Muir-Torre syndrome
 - E. Epidermal nevus syndrome
3. Which of the following entities is virtually pathognomonic of neurofibromatosis 1?
 - A. Plexiform neurofibroma
 - B. Café-au-lait macule
 - C. Optic glioma
 - D. Sphenoid dysplasia
 - E. Iris hamartoma
4. Which one of the following tumors is S-100 protein immunostaining negative?
 - A. Granular cell tumor
 - B. Cellular neurothekeoma
 - C. Adenoid cystic carcinoma
 - D. Schwannoma
 - E. Melanoma
5. A patient with multiple sebaceous adenomas should be screened with which of the following examinations?
 - A. CT scan of the chest
 - B. Retinal examination
 - C. Mammogram
 - D. Renal ultrasound
 - E. Colonoscopy
6. Which of the following is associated with Darier's disease?
 - A. Clear cell syringoma
 - B. Acrokeratosis verruciformis of Hopf
 - C. Syringocystadenoma papilliferum
 - D. Fibrofolliculoma
 - E. Sebaceous adenoma

7. Which of the following malignant tumors is least likely to metastasize?
 - A. Porocarcinoma
 - B. Malignant chondroid syringoma
 - C. Dermatofibrosarcoma protuberans
 - D. Sebaceous carcinoma
 - E. Merkel cell carcinoma
8. A 14-year-old boy presents with bilateral angiofibromas near the nasal labial folds. A characteristic dental finding in this patient would be the following:
 - A. Congenital missing teeth
 - B. Odontodysplasia
 - C. Hutchinson's teeth
 - D. Enamel teeth pits
 - E. Odontogenic cysts
9. Which is the most common tumor arising in association with nevus sebaceus of Jadassohn?
 - A. Basal cell carcinoma
 - B. Apocrine carcinoma
 - C. Sebaceous carcinoma
 - D. Syringocystadenoma papilliferum
 - E. Sebaceoma
10. Which syndrome is characterized by the development of multiple trichoepitheliomas and cylindromas?
 - A. Rombo syndrome
 - B. Birt-Hogg-Dube syndrome
 - C. Bazex syndrome
 - D. Cowden syndrome
 - E. Brooke-Spiegler syndrome
11. Which epithelial neoplasm is usually *not associated* with Borst-Jadassohn phenomenon?
 - A. Actinic keratosis
 - B. Squamous cell carcinoma
 - C. Seborrheic keratosis
 - D. Basal cell carcinoma
 - E. Hidroacanthoma simplex
2. C. The young girl is presenting with a rare case of eruptive syringoma, known to be associated with Down syndrome.
3. A. Plexiform neurofibroma is a peripheral nerve tumor that clinically feels like a "bag of worms" on palpation. It is virtually pathognomonic of neurofibromatosis 1 (NF-1). Sphenoid dysplasia is a prominent facial feature of NF1, but not entirely pathognomonic. The other entities are associated with NF1, but can be seen in other conditions as well.
4. B. Although dermal nerve sheath myxoma (neurothekeoma) stains positive for S-100 protein, cellular neurothekeoma does not.
5. E. Muir-Torre syndrome is an autosomal dominant cancer predisposition condition defined by one or more sebaceous neoplasms (sebaceous adenoma, sebaceous epithelioma, or rarely sebaceous carcinoma) and one or more visceral malignancies, including colon cancer. Patients and first-degree relatives should be screened by colonoscopy as colonic adenocarcinomas may precede the development of cutaneous tumors.
6. B. Acrokeratosis verruciformis of Hopf is an autosomal dominant disorder that can be associated with Darier's disease. Clear cell syringoma is associated with diabetes, while syringocystadenoma papilliferum and fibrofolliculoma are seen in nevus sebaceus and Birt-Hogg-Dube syndrome, respectively. Sebaceous adenoma can be associated with Muir-Torre syndrome.
7. C. Dermatofibrosarcoma protuberans (DFSP) generally do not metastasize unless they become fibrosarcomatous. Malignant chondroid syringoma metastasizes in up to 60% of cases, while sebaceous carcinoma metastasizes in 14–25% of cases. Porocarcinoma and Merkel cell carcinoma also have significant metastatic potential.
8. D. The adolescent boy is presenting with tuberous sclerosis, an autosomal dominant condition characterized by multiple, bilateral angiofibromas near the nasal labial folds at puberty in addition to periungual fibromas, enamel teeth pits, central nervous system defects (epilepsy and low intelligence), and ophthalmological, cardiac, and pulmonary disorders. Hutchinson's teeth are seen in congenital syphilis and odontogenic cysts are found in Gorlin syndrome.
9. D. Various types of appendageal tumors may develop in association with nevus sebaceus of Jadassohn. They include: syringocystadenoma papilliferum (8–10%), trichoblastoma (5%), and rarely trichilemmoma (2–3%), sebaceoma (2–3%), syringoma, apocrine cystadenoma, hidradenoma or keratoacanthoma. Basaloid epithelial proliferations resembling basal cell carcinoma can be identified

Answers

1. D. Cowden's syndrome is an autosomal dominant disorder variable expression that results from a mutation in the *PTEN* gene on chromosome arm 10q resulting in a dysfunctional tyrosine kinase phosphatase enzyme. The clinical picture includes hamartomatous neoplasms of skin and mucosa (mucosal papillomatosis, oral-plantar keratosis), GI tract, bones, central nervous system, eyes and genitourinary tract. It can be associated with several types of malignancy: breast, endometrial and thyroid carcinomas.

- in 5–7% of cases of nevus sebaceus. Malignant tumors (apocrine carcinoma, basal cell carcinoma, squamous cell carcinoma) have been described to arise seldom in association with nevus sebaceus.
10. E. Autosomal dominant disease (*CYLD* gene on chromosome 9p21) characterized by the development of multiple trichoepitheliomas and cylindromas
 11. D. Borst-Jadassohn phenomenon is currently regarded as a histopathological appearance rather than a precise clinicopathological entity (was formerly known as intraepidermal epithelioma of Borst-Jadassohn). It is characterized by intraepithelial nests of clonal keratinocytic proliferation in the background of a seborrheic keratosis, actinic keratosis, hidroacanthoma simplex, intraepidermal eccrine poroma, and Bowen's disease (squamous cell carcinoma in situ).

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MELANOMA AND NON-MELANOMA SKIN CANCER

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NON-MELANOMA SKIN CANCER

Tumor Suppressor Genes

- Negative cancer regulators
- Cause apoptosis of DNA-damaged cells and blocks cell division
- Encode cell-cycle regulators, adhesion molecules, DNA repair enzymes, or signal transduction pathway molecules
- Are recessive
- Even if heterozygosity exists, tumor suppression continues
- p53 (Fig. 12-1)
 - Found on chromosome 17p
 - Mutation of a single copy of the two copies is enough for the deleterious effect
 - Most common cancer mutation (mutated in one-half of all human cancers)
 - Ninety percent of squamous cell carcinomas (SCCs) and in most basal cell carcinomas (BCCs) and actinic keratosis
 - Extrinsic and intrinsic apoptotic pathways
 - Lead to the activation of the aspartate-specific cysteine proteases (caspases) that mediate apoptosis
 - *Extrinsic pathway*
 - ▲ Involves engagement of particular “death” receptors that belong to the tumor necrosis factor receptor (TNF-R) family (e.g., Fas, DR5, and PERP)
 - ▲ Also causes the formation of the death-inducing signaling-complex (DISC)
 - Intrinsic pathway
 - ▲ Triggered in response to DNA damage

- ▲ Associated with mitochondrial depolarization and release of cytochrome c from the mitochondrial intermembrane space into the cytoplasm
- ▲ Cytochrome c, apoptotic protease-activating factor 1 (APAF-1), and procaspase-9 form a complex termed the *apoptosome* (caspase-9 is activated and promotes activation of caspase-3, caspase-6, and caspase-7)
- Mutation is not the only way to inactivate tumor suppressor genes; function also can be blocked by methylation of their promoter

Oncogenes

- Genes with growth-promoting activity
- Mutated gene causes cellular products to become constitutively active
- Are dominant
- If a normal gene (protooncogene) is present at a locus along with one mutated gene (oncogene), the abnormal product takes control
- May derive from viruses (e.g., *Src*, *ras*, *cmyc*)

Carcinogenesis

- Two-hit theory of Knudsen
 - First: inheriting a defect in the familial form (5% to 10% of cancers result from germ-line mutations) or exposure to a carcinogen
 - Second: ongoing exposure to the carcinogen that acts as a tumor promoter or co-carcinogen
- Repeated assault on the DNA leads to mutations that cause the cell cycle to lose control
- Mutations from ultraviolet B (UV-B) light cause cytosine (C) to change to thymine (T)

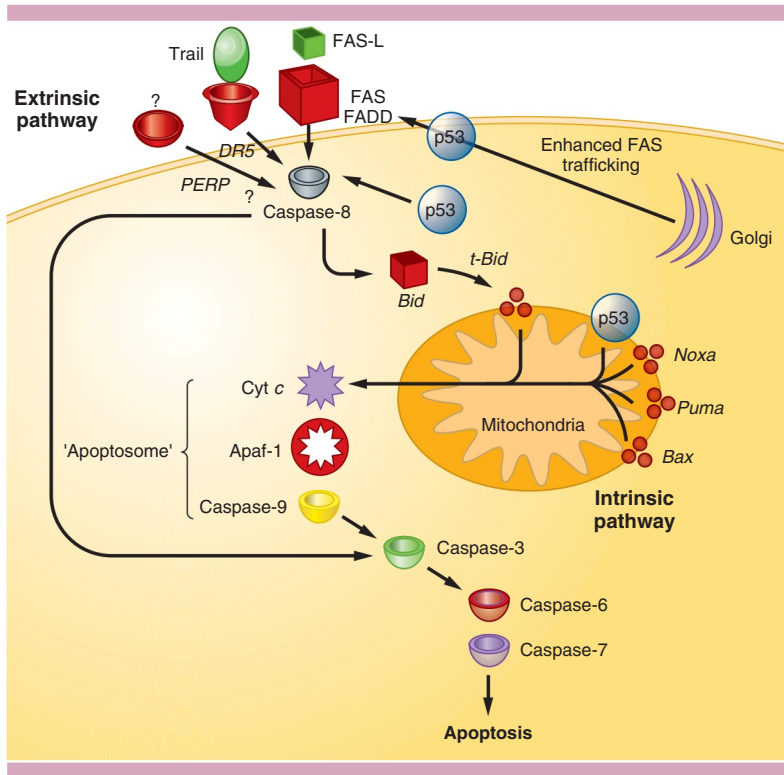


FIGURE 12-1 A model for p53-mediated apoptosis.

AP-1 (Activating Protein-1)

- Negative regulator for procollagen transcription; blocked by retinoids
- Collective term referring to dimeric transcription factors composed of *Jun*, *Fos*, or *ATF* subunits (protooncogenes)
- UV-B induces AP-1 binding to DNA at the AP-1-binding site
- AP-1 upregulates mRNA expression for gelatinase and collagenase
- AP-1 blocks collagen gene expression in dermal fibroblasts
- AP-1 proteins regulate the expression and function of cell-cycle regulators such as p53

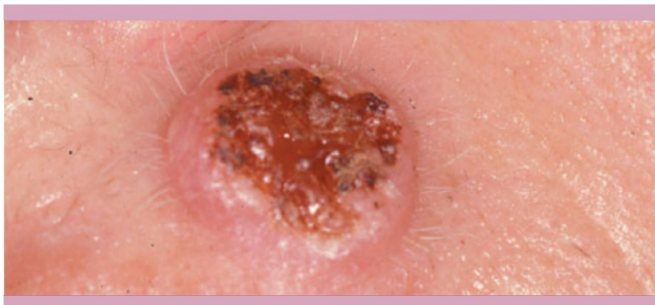


FIGURE 12-2 Basal cell carcinoma. (Courtesy of Dr. Adelaide Hebert.)

- Absence of c-Jun results in elevated expression of the tumor suppressor gene *p53*
- Overexpression of c-Jun suppresses p53

Basal Cell Carcinoma

- Neoplasm derived from non-keratinizing cells that originate in the basal cell layer
- Most common malignancy in humans
- Mutations in the *p53* tumor suppressor gene, which resides on chromosome 17p
- Clinical and histologic subtypes
 - Nodular (Fig. 12-2)
 - Pigmented (Fig. 12-3)
 - Cystic
 - Superficial (Fig. 12-4)
 - Micronodular
 - Morpheaform/sclerosing and infiltrating
- Risk Factors/Etiological factors
 - Ultraviolet radiation
 - Other radiation: x-rays and Grenz rays
 - Arsenic exposure
 - Xeroderma pigmentosum
- **Nevoid BCC syndrome** (also known as basal cell nevus syndrome or Gorlin syndrome)
 - Autosomal dominant; abnormalities in the *patched (PTCH)* gene, chromosome 9
 - 1 in 60,000–120,000
 - Complete penetrance with variable expressivity



FIGURE 12-3 Pigmented basal cell carcinoma.
(Courtesy of Dr. Asra Ali.)



FIGURE 12-4 Superficial basal cell carcinoma.
(Courtesy of Dr. Asra Ali.)

- Starts at an early age (starting at age 20 or earlier)
- Characteristic facies: broad nasal root, frontal bossing, hypertelorism
- Multiple BCCs
- Opacity and cataract or glaucoma
- Odontogenic keratocysts
- Palmoplantar pitting
- Intracranial calcification; calcification of the falx
- Bifid ribs
- Various tumors: medulloblastomas, meningioma, fetal rhabdomyoma, ameloblastoma, ovarian fibromas
- Acrokeratosis paraneoplastica of Bazex
- Bazex-Dupre-Christol syndrome
 - X-linked dominant
 - Follicular atrophoderma (“ice pick” marks, especially on dorsal hands)
 - Multiple BCCs: face, the neck, and the upper part of the trunk
 - Local anhidrosis/hypohidrosis
 - Hypotrichosis
 - Respiratory tract or digestive tract carcinomas

- Rombo syndrome
 - Autosomal dominant
 - Milia
 - Hypertrichosis
 - Trichoepitheliomas
 - Peripheral vasodilation
- Course
 - Incidence of new NMSC after initial skin cancer diagnosis
 - 35% at 3 years
 - 50% at 5 years
- Staging
 - TNM classification
 - Stage 0: Tis, N0, M0
 - Stage I: T1, N0, M0
 - Stage II: T2, N0, M0; T3, N0, M0
 - Stage III: T4, N0, M0; any T, N1, M0
 - Stage IV: any T, any N, M1
- Low-risk tumors
 - Borders are well defined; primary tumor; nonimmunosuppressed; nodular or superficial subtype
 - Trunk and extremities: < 2 cm
 - Cheek/forehead/scalp/neck: < 1 cm
- High-risk tumors
 - Aggressive histology: recurrent, micronodular, metatypical, sclerosing/morpheaform, infiltrative, perineural
 - Recurrent, immunosuppressed, BCCNS, ill defined borders, setting of irradiated skin
 - Trunk and Extreities: > 2 centimeters
 - Cheek/forehead/scalp/neck: ≥ 1 cm
 - Mask areas of face [central face (nose, periorbital, cutaneous and mucosal lips, chin), periauricular, temple]
- Treatment
 - Electrodesiccation and curettage
 - Cryotherapy
 - Imiquimod cream
 - Photodynamic therapy (PDT)
 - Radiation therapy: nonsurgical candidates, debilitated patients
 - Excision
 - Mohs micrographic surgery
 - Intralesional interferon

Squamous Cell Carcinoma In Situ **[Bowen’s Disease (BD)]**

- Malignant tumor of keratinocytes (Fig 12-5)
- Neoplastic process limited to the epidermis
- *Vulvar BD* associated with increased risk of uterine, cervical, and vaginal cancer, possibly due to HPV infection
- *Erythroplasia of Querat (EQ)* occurs on mucosal surfaces of penis in uncircumscised males

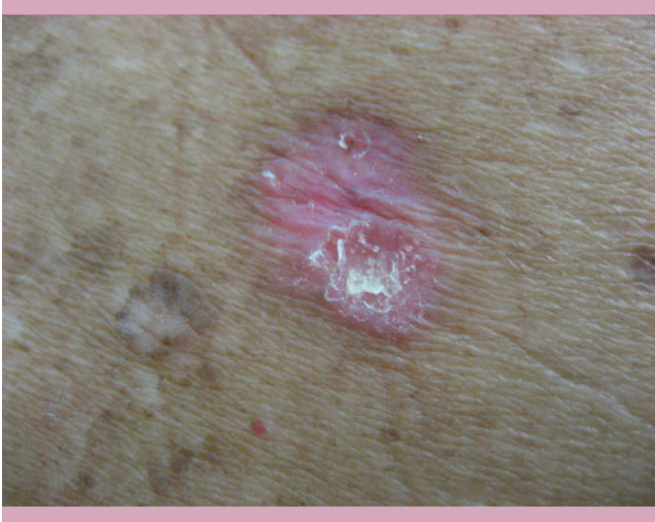


FIGURE 12-5 Bowen's disease. (Courtesy of Dr. Asra Ali.)

- Co-infection with HPV subtypes 8, 16, 39, 51
- Progresses to invasive SCC in approximately 10%
- Preventive measures: circumcision and hygiene
- Solitary, rapidly growing, dome-shaped papulonodule with a central, horn-filled, craterlike depression

Leukoplakia

- Most common precancerous lesion of oral mucosa
- White plaque on oral mucosa that cannot be rubbed off
- Potential to become oral SCC
- Risk factors: tobacco, alcohol, HPV

Erythroplakia

- Red macule or patch of oral mucosa
- Least common but greatest potential to become oral SCC
- Treatment: complete excision or Mohs surgery

Squamous Cell Carcinoma

- Second most common form of skin cancer
- Malignant tumor of keratinocytes
- Predisposing conditions
 - Immunosuppression (especially solid-organ transplant recipients, chronic lymphocytic lymphoma, human immunodeficiency virus infection)
 - Psoralen and ultraviolet A light (> 300 treatments)
 - Chemical carcinogens (tar, soot, arsenic)
 - Smoking
 - Genetic syndromes (i.e., xeroderma pigmentosum)



FIGURE 12-6 Keratoacanthoma (Courtesy of Dr. Asra Ali.)

- Chronic inflammatory conditions (i.e., discoid lupus erythematosus, erosive oral lichen planus, morphea, lichen sclerosus)
- Chronic infections (i.e., osteomyelitis)
- Chronic scarring conditions (i.e., burn scars, chronic ulcers, thermal injury, irradiated skin [ionizing radiation])
- Periungual SCC—often associated with HPV 16
- Keratoacanthoma (Fig. 12-6)
 - Well-differentiated SCC
 - Solitary, rapidly growing, dome-shaped papulonodule with a central, horn-filled, craterlike depression
- Verrucous carcinoma
 - Rare, indolent form of SCC that presents as an exophytic verrucous tumor
 - Oral cavity (oral florid papillomatosis)
 - Foot (epithelioma cuniculatum)
 - Genitals (giant condyloma of Buschke and Lowenstein)
- High-risk SCCs and metastatic rate
 - Metastasis to primary or first echelon draining lymph nodes
 - Size > 2 cm
 - External ear: 11%
 - Lip: 10% to 14%
 - Histologic risk factors: depth > 4 mm or Clark level IV, poorly differentiated or spindle-cell type, lack of inflammatory infiltration
- Marjolin ulcer
 - SCC arising in a chronic site of inflammation: old burn scar or a draining sinus tract
 - Organ transplant patient metastatic rate is 18 to 36 times that of the general population

- Perineural invasion: 35%; local recurrence rate as high as 47%
- Treatment
 - Small, low-risk lesions in non-surgical candidates
 - Cryosurgery
 - Electrodesiccation and curettage
 - Photodynamic therapy (PDT)
 - Topical therapy (imiquimod, fluorouracil)
 - Standard treatment
 - Excision
 - Radiation
 - Mohs' micrographic surgery
 - Patients with regional disease
 - Focused neck dissection
 - Superficial parotidectomy
 - Adjuvant radiation therapy
 - Primary radiation if inoperable tumor
 - Five-year survival for patients with metastases 26.8%

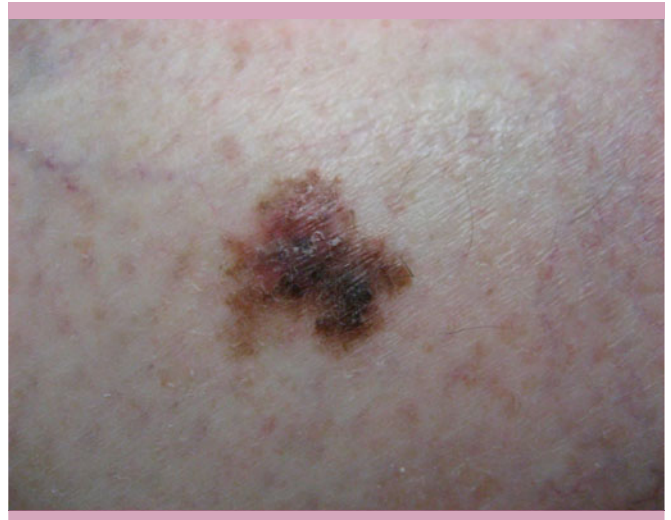


FIGURE 12-7 Superficial spreading melanoma. (Courtesy of Dr. Asra Ali.)

MELANOMA

- Accounts for 4% of all skin cancer; accounts for 79% of deaths related to skin cancer
- More than 50% of cases are believed to arise de novo
- 10% to 20% of all patients with melanoma have a family history of melanoma
- Risk factors for cutaneous melanoma
 - Dysplastic nevi in familial melanoma
 - Greater than 50 nevi 2 mm or greater in diameter
 - One family member with melanoma
 - Previous history of melanoma
 - History of acute, severe, blistering sunburns
 - Freckling
- Clinical types
 - *Superficial spreading* (Fig. 12-7): most common type (70%)
 - *Lentigo maligna* (Fig. 12-8): 10% of all melanomas
 - *Acrall lentiginous melanoma (ALM)*
 - 2% to 8% of melanoma in Caucasians
 - 29% to 72% of melanoma in dark-skinned individuals
 - *Amelanotic melanoma*: < 2% of melanomas
 - Mucosal: approximately 3%
 - *Nodular*: 10% to 15%
- Genes implicated in the development of melanoma
 - Cyclin-dependent kinase inhibitor 2A (CDKN2A) resides on chromosome 9p
 - Cell-cycle regulatory gene
 - Protein target: inhibitor of cyclin-dependent kinase 4 (CDK4)
 - Encodes two distinct gene products that are regulators of cell division cycle

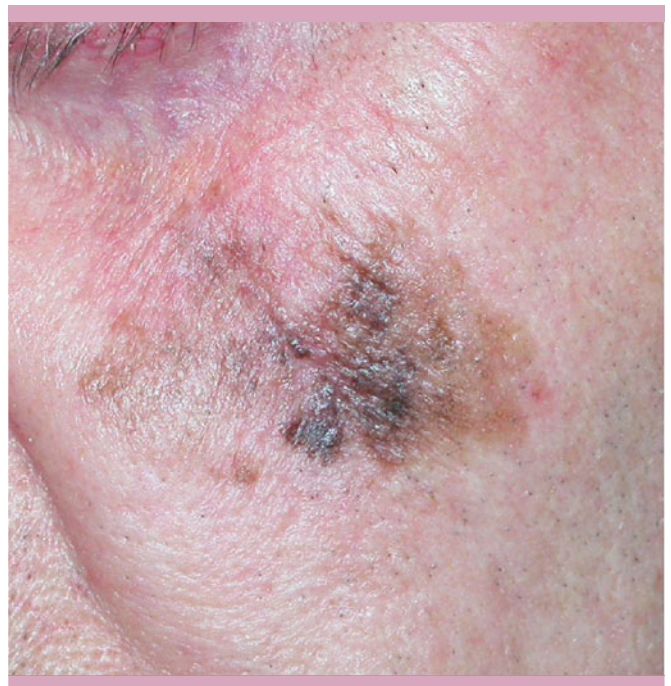


FIGURE 12-8 Lentigo melenamo. (Reproduced with permission from Wolff, et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. © 2008. New York: McGraw-Hill; 2008.)

- ▲ p16(INK4a): INK4 proteins inhibit complexes formed by the cell cycle kinases CDK4 and CDK6 and the D-type cyclins
- ▲ p19 (ARF): acts on the p53 pathway
- Associated with 25% to 60% of familial melanoma

- Prognosis
 - Ulceration, Breslow depth, and tumor thickness, important histologic determinants
 - Breslow depth: measured vertically in millimeters from the top of the granular layer (or base of superficial ulceration) to the deepest point of tumor involvement
- Immunohistochemical staining
 - *Homatropine methylbromide 45* (HMB-45)
 - Spindle cell and desmoplastic variants fail to react with HMB-45
 - Shown to react with other neural crest-derived tumors and occasionally with adenocarcinomas and other neoplasms
 - Specificity for detecting melanoma is 96.9%
 - *S-100*: specificity of 70%
 - *Microphthalmia transcription factor (Mitf)*: nuclear transcription factor critical for melanocyte development and survival
 - *Tyrosinase*: enzyme involved in the early stages of melanin production
 - *Melan-A* (or MART-1)
 - Product of the *MART-1* gene
 - Cytoplasmic protein that is expressed in mature melanocytes
 - *Ki67*: Proliferating cell nuclear antigen
- Revised AJCC TNM classification and staging
 - *T classification*
 - T1: ≤ 1.0 mm
 - ▲ a: without ulceration
 - ▲ b: with ulceration or level IV or V
 - T2: 1.01–2.0 mm
 - ▲ a: without ulceration
 - ▲ b: with ulceration
 - T3: 2.01–4.0 mm
 - ▲ a: without ulceration
 - ▲ b: with ulceration
 - T4: > 4.0 mm
 - ▲ a: without ulceration
 - ▲ b: with ulceration
 - N classification
 - N1: one lymph node
 - ▲ a: micrometastasis
 - ▲ b: macrometastasis
 - N2: 2–3 lymph nodes
 - ▲ a: micrometastasis
 - ▲ b: macrometastasis
 - ▲ c: in-transit metastasis(-es)/satellite(s) without metastatic lymph nodes
 - N3: 4 or greater metastatic lymph nodes, matted lymph nodes, or combinations of in-transit metastasis(-es)/satellite(s) and metastatic lymph nodes
 - M classification
 - M1: distant skin, subcutaneous, or lymph node metastasis
 - M2: lung metastasis
 - M3: all other visceral or any distant metastasis with elevated LDH
- Treatment: wide local excision
 - Tumors ≤ 1 mm depth: 1 cm margin
 - Tumors 1 to 4-mm in depth: 2–3 cm margins
 - Overall survival rates: Delayed lymph node dissection was not statistically significant compared with immediate node dissection
- Sentinel lymph node biopsy/lymphatic mapping
 - Absence of clinically palpable nodes
 - Thicker melanomas (≥ 1 mm in depth)
 - Determines presence of micrometastasis; if positive sentinel lymph node, then therapeutic lymph node dissection proceeds
 - Lymphoscintigraphy: preoperative radiographic mapping and vital blue dye injection around the primary melanoma or biopsy scar; isosulfan blue dye plus sulfur-colloid-labeled technetium isotope increases accuracy of finding sentinel node
 - Performed at the time of wide local excision or re-excision
 - Identifies and removes the initial draining regional node(s)
 - Yields prognostic information but no evidence SLN; removal improves survival (current studies ongoing)
- Risk of primary tumor recurrence
 - Desmoplastic subtype
 - Positive microscopic margins
 - Recurrent disease
 - Thick primary lesions with ulceration or satellitosis
- High risk of nodal relapse
 - Extracapsular extension
 - Involvement of four or more lymph nodes
 - Lymph nodes measuring at least 3 cm
 - Cervical lymph node location
 - Recurrent disease
- Interferon alfa (IFN- α)
 - Approved by the Food and Drug Administration (FDA) for treatment of melanoma
 - Adjuvant treatment after excision in patients who are free of disease but are at high risk for recurrence: stages IIB and III
 - For primary tumors > 4 mm depth and regional nodal disease
 - Binds to cell surface receptors, interacting with specific gene sites in both normal and neoplastic cells
 - Modulates the expression of host natural killer cells, T cells, monocytes, dendritic cells, and class I and II major histocompatibility (MHC) antigens in both neoplastic and nonneoplastic host tissues
 - Shown to have a growth-inhibitory effect when added to tumor cells in vitro

- 11% increase (26% to 37%) in survival rates at 5 years in the IFN- α treatment group compared with the observation arm
- Interleukin 2 (IL-2): indirectly causes tumor cell lysis by proliferating and activating cytotoxic T-lymphocytes
- Dacarbazine (DTIC)
 - Approved by FDA for treatment of melanoma
 - Response rate of 10% to 20%
 - Combination therapy
 - Cisplatin, vinblastine, and DTIC (CVD) regimen
 - Cisplatin, DTIC, carmustine, and tamoxifen
- Radiation
 - Adjuvant treatment of regional node metastasis with extracapsular extension
 - Palliative treatment of distant metastatic disease: bone or brain
- Factors predicting response to treatment:
 - Good performance status
 - Soft-tissue disease or only a few visceral metastases
 - Age younger than 65 years
 - No prior chemotherapy
 - Normal hepatic and renal function
 - Normal complete blood count (CBC)
 - Absence of central nervous system metastases
- Melanoma vaccines
 - Active immunization: elicits specific or nonspecific reactivity against a tumor antigen by stimulating the patient's own immune system
 - Passive immunization: administration of antitumor antibodies or cells against a tumor antigen
 - Autologous (killed cell and recombinant types): Heat shock protein extracts purified from autologous tumor cells also have been shown to have antitumor reactivity
 - Allogeneic
 - Generated using established stable cultured cell lines derived from tumors previously obtained from patients
 - Shed from tumor
 - Antigen-directed or genetically engineered
 - Polyvalent or univalent
 - Whole-cell preparations: immunizing with diverse antigens that are present on the tumor surface without knowing the exact antigen(s)
 - Gangliosides: tumor antigens that are created synthetically: GM2
 - Peptides/proteins
 - Direct loading of peptide fragments onto APCs
 - Antigenic epitopes responsible for eliciting an antitumor response consist of small peptide fragments

- Dendritic cell vaccines
 - Recombinant viral and bacterial vaccines
 - Direct transduction
- Cytokine and growth factor modulation
 - IL-2, interferons (IFN- α , IFN- β , IFN- γ), GM-CSF, and TNF
 - Allow sustained local release of cytokines to enhance a potent local inflammatory response
- DNA and RNA vaccines
 - Induce activation of APCs, which then present antigens to T cells

Merkel Cell Carcinoma (MCC)

- Neuroendocrine carcinoma of the skin
- Mortality rate is approximately 25%
- Most frequent sites: head, neck region, and extremities
- Located in or near the basal layer of the epidermis
- Clinical
 - Painless, indurated, solitary dermal nodule, slightly erythematous to deeply violaceous color
 - Regional lymph nodes at presentation: 10% to 45%
 - Regional lymph node metastases during course of disease: 50% and 75%
- Distant metastases: 50%
- Common sites: lymph nodes, liver, bone, brain, lung, and skin
- Local recurrence develops in 25% to 44% after primary tumor excision
- Histology: three distinct subtypes
 - Trabecular: interconnecting strands of tumor cells in the dermis, with grouping of cells that appear as glands or neural rosettes
 - Intermediate: neoplastic cells in solid nests, most common pattern
 - Diffuse pattern: tumor cells interspersed among dermal collagen bundles
- Staging: classification based on clinical presentation
 - Stage IA: primary tumor ≤ 2 cm, with no evidence of spread to lymph nodes or distant sites
 - Stage IB: primary tumor > 2 cm, with no evidence of spread to lymph nodes or distant sites
 - Stage II: regional node involvement but no evidence of distant metastases
 - Stage III: presence of systemic metastases beyond the regional lymph nodes
- Treatment
 - Stage I
 - Wide local excision: 2-cm margins
 - Elective lymph node dissection (ELND)
 - ▲ Larger tumors, tumors with greater than 10 mitoses per high-power field, lymphatic or vascular invasion, and the small cell histologic subtypes

- Sentinel lymph node (SLN) biopsy
 - ▲ MCC sites with indeterminate lymphatic drainage
 - ▲ Effective in preventing short-term regional nodal recurrence
- Adjuvant radiation therapy
 - ▲ Primary site and to the regional lymph node basin
 - ▲ Larger tumors, tumors with lymphatic invasion, tumors approaching the surgical margins of resection, and locally unresectable tumors
 - ▲ 50 Gy to the surgical bed and the draining regional lymphatics: delivered in 2-Gy fractions
- Stage II
 - Wide local excision of the primary tumor
 - Regional lymph node dissection
 - Adjuvant radiation therapy: primary site and to the regional lymph node basin
 - ▲ Larger tumors, tumors with lymphatic invasion, tumors approaching the surgical margins of resection, and locally unresectable tumors
 - ▲ 50 Gy to the surgical bed and the draining regional lymphatics: delivered in 2-Gy fractions
 - Adjuvant chemotherapy: regimens similar to patients with small cell lung cancer
 - ▲ Cyclophosphamide, doxorubicin, and vincristine and etoposide plus cisplatin are the most commonly used regimens
 - ▲ Impact on survival uncertain
- Stage III
 - Chemotherapy: unresectable recurrent tumors
 - Regional lymph node dissection and adjuvant radiation therapy if the regional draining nodes have not been treated previously
 - Adjuvant radiation therapy: site of recurrence as well as regional lymph node beds
- Aggressive variations
 - Sézary syndrome (SS): leukemic variant of MF
 - Adult T-cell leukemia/lymphoma
 - Extranodal NK/T-cell lymphoma, nasal type
 - Primary cutaneous peripheral T-cell lymphoma, unspecified
 - Primary cutaneous aggressive epidermotropic CD8 T-cell lymphoma
 - Cutaneous γ/δ T-cell lymphoma
- Mycosis fungoides (MF)/Sézary syndrome (SS) (Figs. 12-9, 12-10, 12-11)
 - Appearance: patches/plaques/tumors with various shape, color, and scales +/- erythroderma (diffuse skin erythema of > 80% body surface area [BSA])
 - Classic: poikilodermatous MF (epidermal atrophy often with telangiectasia, pigment alteration)
 - Atypical: hypopigmented/vitiliginous MF, granulomatous MF, granulomatous slack skin, Worringer-Kolopp disease (pagetoid reticulosis), folliculocentric MF, pigmented purpuric eruption-like MF, interstitial MF, and papular MF
 - Location: “bathing trunk” distribution in non-sun exposed areas
 - Characterization: MF can lead to SS; SS can lead to MF; or both can arise de novo
 - Histology (Figs. 12-12, 12-13): proliferation of CD4 + CD45RO + helper T cells that often lack normal antigens (CD7-, CD26-) and make a superficial lymphoid infiltrate with epidermotropism without spongiosis

Cutaneous T-Cell Lymphoma (CTCL)

- Definition: diverse group of non-Hodgkin’s lymphomas presenting as skin lesions containing malignant, skin-homing T-lymphocytes
- Indolent variations
 - Mycosis fungoides (MF): most common
 - Primary cutaneous CD30 lymphoproliferative disorders
 - Primary cutaneous anaplastic large cell lymphoma (ALCL)
 - Lymphomatoid papulosis (LyP)
 - Subcutaneous panniculitis-like T-cell lymphoma
 - Primary cutaneous CD4 small/medium-sized pleomorphic T-cell lymphoma



FIGURE 12-9 Mycosis fungoides patches and plaques. (Courtesy of Dr. Madeline Duvic.)



FIGURE 12-10 Erythrodermic mycosis fungoides and or Sézary syndrome. (Courtesy of Dr. Madeline Duvic.)



FIGURE 12-11 Mycosis fungoides tumor stage. (Courtesy of Dr. Madeline Duvic.)

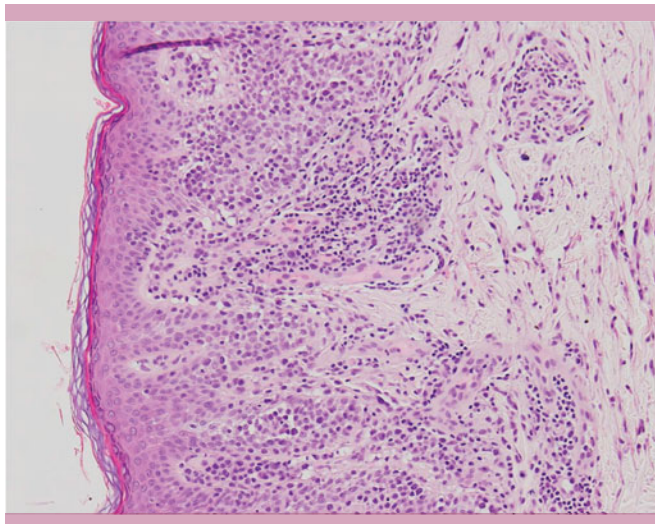


FIGURE 12-12 Mycosis fungoides histology. (Courtesy of Dr. Madeline Duvic.)

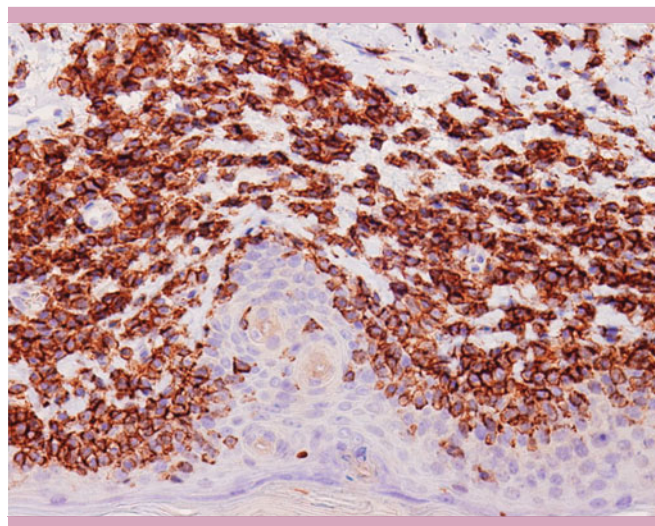


FIGURE 12-13 Mycosis fungoides cd4 stain. (Courtesy of Dr. Madeline Duvic.)

+/- lymphoid atypia; +/- clonal T-cell receptor (TCR) gene rearrangement; +/- Pautrier's microabscesses (collections of neoplastic lymphocytes). {Note: In SS, atypical cells surround venules because the epidermotropism is lost unless the patient had prior MF.}

- Algorithm to diagnose early MF (add up points):
 - Clinical criteria: persistent and/or progressive patches and plaques plus:
 - ▲ Non-sun-exposed location
 - ▲ Size/shape variation
 - ▲ Poikiloderma
 - ▲ Any 2 = 2 points; any 1 = 1 point (cannot give 3 points)

- Histopathologic criteria: superficial lymphoid infiltrate plus:
 - ▲ Epidermotropism without spongiosis
 - ▲ Lymphoid atypia (enlarged hyperchromatic nuclei and irregular or cerebriform nuclear contours)
 - ▲ Both = 2 points; either = 1 point
- Molecular/biologic: clonal TCR gene rearrangement; 1 point if present
- Immunopathologic:
 - ▲ CCD2,3,5 < 50% T cells
 - ▲ CD7 < 10% T cells
 - ▲ Epidermal discordance from expression of CD2,3,5 or 7 on dermal T cells
 - ▲ One or more criteria = 1 point
 - ▲ Total: need at least 4 points to diagnose MF
- ▲ 3 = partial effacement of LN architecture; many atypical cerebriform mononuclear cells
- ▲ 4 = complete effacement of LN architecture
- NCI LN grade 4: partial/complete effacement of nodal architecture by atypical lymphocytes or frankly neoplastic cells
- Nx: clinically abnormal; no histologic confirmation
- Visceral (M):
 - M0: no visceral organ involvement
 - M1: visceral involvement (with positive biopsy, except for splenomegally; specify organ)
 - Bone marrow: no current system in place to account for involvement; some consider bone marrow involvement as stage IVB
 - Blood (B):
 - ▲ Sézary cells: lymphocytes with hyperconvoluted cerebriform nuclei; + /- loss of CD7/CD26; + /- TCR clonal rearrangement; measured by peripheral blood flow cytometry
 - ▲ B0: insignificant blood involvement: < 5% peripheral blood lymphocytes are atypical (Sézary) cells
 - ▲ B1: low blood tumor burden: > 5% but does not fit B2 criteria
 - ▲ B2: (Sézary syndrome): high blood tumor burden: $\geq 1000/\mu\text{l}$ Sézary cells with TCR clonal rearrangement OR one of the following: CD4/CD8 ratio ≥ 10 or \uparrow CD4 + / CD7- or \uparrow CD4 + / CD26-
- Staging: determines later treatment options
 - IA: T1 N0 M0 B0-1: limited patch/plaque (< 10% BSA)
 - IB: T2 N0 M0 B0-1: generalized patch/plaque ($\geq 10\%$ but < 80% BSA)
 - IIA: T1-2 N1-2 M0 B0-1
 - IIB: T3 N0-2 M0 B0-1: tumors
 - IIIA: T4 N0-2 M0 B0: erythroderma without blood involvement
 - IIIB: T4 N0-2 M0 B1: erythroderma with low blood tumor burden
 - IVA1: T1-4 N0-2 M0 B2: SS (high blood tumor burden)
 - IVA2: T1-4 N3 M0 B0-2: very abnormal nodes
 - IVB: T1-4 N0-3 M1 B0-2: visceral involvement
- Diagnostic testing
 - Skin biopsy: select the most indurated area that has not been treated for at least two weeks, ✓ CD30 + (for ALCL, LyP, or large cell transformation (LCT)), ✓ CD2,3,4,5,7,8 and TCR rearrangements (polymerase chain reaction or western blot)

TNM Definitions: Updated in 2007

- Skin (T):
 - T1: limited patches/papules/plaques < 10% BSA
 - T2: patches/papules/plaques $\geq 10\%$ and < 80% BSA
 - T3: one or more tumors
 - T4: erythroderma (confluent erythema $\geq 80\%$ BSA)
- Node (N):
 - Abnormal lymph node: > 1.5 cm in longest transverse diameter or with abnormal palpable qualities (firm, irregular, fixed, clustered); sample by core aspiration or excisional biopsy; classify according to lymph node (LN) pathology guidelines (Dutch system or NCI-VA classification)
 - N0: no clinically abnormal peripheral lymph nodes
 - N1: clinically abnormal; + /- TCR clone Histopathology:
 - Dutch grade 1 (dermatopathic lymphadenopathy (DL))
 - NCI LN grade 0-2:
 - ▲ 0 = no atypical lymphocytes
 - ▲ 1 = occasional/isolated atypical lymphocytes
 - ▲ 2 = many atypical lymphocytes or in 3-6 cell clusters
 - N2: clinically abnormal; + /- TCR clone Histopathology:
 - Dutch grade 2 (DL; early involvement of MF)
 - NCI LN grade 3: aggregates of atypical lymphocytes; nodal architecture preserved
 - N3: clinically abnormal; + /- TCR clone Histopathology:
 - Dutch grades 3-4:

- Blood: CBC, LFTs, LDH, magnesium, chemistries, flow cytometry (✓ CD4 + CD26+ cells, CD3-CD4 + cells, and CD3-CD8 + cells), ✓ HIV/HTLV, ✓ immunoglobulins (for advanced patients)
- Imaging
 - Clinically normal lymphadenopathy: CXR or ultrasound to rule out lymphadenopathy
 - Potential lymphadenopathy: CT scans of chest, abdomen, and pelvis (lymphoma screen) + /- FDG-PET scan
- Lymph node biopsy: prefer largest lymph node draining involved skin or node with highest standardized uptake value (SUV) on PET scan; if all nodes equal: cervical > axillary > inguinal.
- Bone marrow biopsy: if B2 blood involvement or unexplainable hematologic abnormalities
- Prognosis:
 - Positive: ↑CD8 + cells on biopsy or on flow cytometry, earlier stages rarely have progression to later stages
 - Negative: large cell transformation (LCT) within 2 years of diagnosis, ↓CD8 + cells, increased age, WBC > 20,000, ↑LDH
- Treatment: (for latest info: www.nccn.org)
 - [* = experimental]
 - Skin-directed therapy
 - Use alone for early stage (IA – IIA) disease with only cutaneous involvement
 - Use in combination with systemic therapy or for adjuvant/palliative purposes in any stage
 - Topical corticosteroids: class I-III
 - Topical retinoids: bexarotene/tazarotene/aldara (anecdotal)
 - Phototherapy
 - ▲ Ultraviolet B (UVB) (290–320nm)/narrow-band UVB (311nm): for patch disease + /- thin plaques
 - ▲ Psoralen + Ultraviolet A (PUVA): for thicker plaques; often in combination with interferon-alpha (IFNα) or oral bexarotene
 - Topical nitrogen mustard ointment 10%/20%*/40%*
 - Electron beam radiation
 - ▲ Spot radiation: for single lesion MF or tumors
 - ▲ Total skin electron beam (TSEB): for generalized extensive skin involvement with severe symptoms; can be palliative; most intense skin-directed therapy
 - Generalized systemic therapies: (no comparative trials exist to guide therapy choices)
 - Reserved for late stage disease (IIB +) or early stage disease refractory to skin-directed therapy
 - Interferon – alpha (IFNα)
 - Oral retinoids/rexinoids: Isotretin/Bexarotene
 - Common combination: PUVA + retinoids (RePUVA)
 - Extracorporeal photopheresis (ECP): phototherapy with leukopheresis (photoactivated 8-methoxypsoralen crosslinks DNA in peripheral blood cells after ex vivo UVA irradiation; then blood reinfused into patients); most commonly used in SS and erythrodermic MF.
 - Histone deacetylase (HDAC) inhibitors: Class I-IV; Vorinostat (FDA approved)/Belinostat*/Panobinostat*/Romidepsin*
 - Pralatrexate:* competitive antagonist for dihydrofolate reductase; like methotrexate but has greater internalization into cells
 - Mono-chemotherapy: gemcitabine/liposomal doxorubicin
 - Combo-chemotherapy: CHOP/CMED/ESHAP (stage IV)
 - Targeted systemic therapies
 - Denileukin diftitox (Ontak®): recombinant IL-2 diphtheria toxin fusion protein targeted to the high and intermediate affinity IL-2 receptor on T-cells → inhibits protein synthesis; biopsy for > 20% CD25 +
 - Alemtuzumab (Campath-H1®):* anti-CD52 monoclonal antibody; targets T, B, and NK cells. Used for erythrodermic MF or SS; not useful for tumors or lymphadenopathy; very immunosuppressive.
 - Zanolimumab (HuMax-CD4®): anti-CD4 monoclonal antibody → blocks receptor-mediated T-cell signaling
 - SGN-30:* anti-CD30 monoclonal antibody (useful in LCT or ALCL/LyP)
 - Forodesine (BCX-177®):* inhibits purine nucleoside phosphorylase (PNP)
 - Symptomatic (anti-pruritic) therapies
 - Diligent skin care (antibiotic soap, acidification with 0.25% vinegar rinses) to rid skin of *Staphylococcus aureus*
 - Anti-histamines, gabapentin, mirtazapine, doxepin
 - Allogenic hematopoietic stem cell transplant (HSCT)
 - Graft-vs-T-cell lymphoma effect; potentially curative.
 - For healthy patients (can tolerate immunosuppression) with advanced disease (IIB +) refractory to all primary and salvage therapy options who have matched donors.
 - May pretreat with TSEB to debulk skin disease prior to HSCT

QUIZ

Questions

- Which of the following is NOT true regarding oncogenes?
 - Oncogenes behave in a recessive fashion
 - Oncogenes may derive from viruses
 - Oncogenes have growth promoting activity
 - Examples of oncogenes includes SRC, WNT, RAS, MYC
- All the following are features of aggressive squamous cell carcinoma EXCEPT:
 - Perineural invasion
 - Spindle-cell differentiation
 - Arising in actinically damaged skin or adjacent to actinic keratosis
 - Greater than 4-mm deep or Clark's level IV/V
- Radiation therapy may be useful in the following settings EXCEPT:
 - Adjuvant therapy for squamous cell carcinoma with perineural invasion
 - Verrucous carcinoma
 - Superficially invasive lesions
 - Adjuvant to excisional surgery in treating residual microscopic disease
- All of the following are features of Rombo syndrome EXCEPT:
 - Multiple basal cell carcinoma
 - X-linked dominant
 - Hypertrichosis
 - Trichoepitheliomas
- A patient with an ulcerated 1.7 millimeter melanoma without nodal or metastatic lesions is:
 - Stage Ia
 - Stage Ib
 - Stage IIa
 - Stage IIB
- Which of the following is a consistent histologic finding for mycosis fungoides?
 - Pautrier's microabscesses
 - Epidermotropism of T lymphocytes
 - Spongiosis
 - Presence of a T-cell receptor gene rearrangement
- All of the following tests are routinely part of the MF staging process except:
 - Skin biopsy of the most indurated area
 - Lymph node biopsy of a 1-cm mobile smooth lymph node
 - Flow cytometry to assess level of blood involvement
 - Bone marrow biopsy in B2 patients
 - Check HIV and HTLV in blood
- A 49-year-old black male with a history of mycosis fungoides stage IB on narrow-band UVB and topical corticosteroids now presents for his 3-month follow-up with a new 1-cm tumor on his right arm and a new palpable 2-cm lymph node in his right axilla. What is the next step?
 - Bone marrow biopsy
 - Change from skin-directed therapies to systemic therapies
 - Biopsy of new axillary lymph node and tumor
 - Reassign to stage IIB (tumor)
 - No change in treatment. Continue to monitor.
- A patient has erythroderma but no blood, visceral, or lymph node involvement. What is the stage?
 - IIa
 - IIb
 - IVA1
 - IVA2
 - IVB
- The most common first line treatment regimen used for SS patients involves:
 - Alemtuzumab (Campath-H1®)
 - Extracorporeal photopheresis (ECP) plus interferon or bexarotene
 - External beam radiation
 - Topical nitrogen mustard
 - PUVA

Answers

- A. Oncogenes behave in a dominant fashion such that if a normal gene (protooncogene) is present at a locus along with one mutated gene (oncogene), the abnormal product takes control.
- C. Poorly differentiated squamous cell carcinomas and those with perineural invasion, spindle-cell features, or depth of infiltration greater than 4 mm have high risk of recurrence and metastases. Squamous cell carcinomas arising in actinically damaged skin are considerably low risk with an average metastatic rate of just over 5%.
- B. Radiation therapy of verrucous carcinoma can lead to anaplastic transformation.

4. B. Rombo syndrome is autosomal dominant. Patients develop multiple basal cell carcinomas, milia, hypertrichosis, trichoepitheliomas, and peripheral vasodilation.
5. C. This is a T2b, N0, M0 melanoma and hence it would be stage IIa.
6. B. The biopsy must show evidence of epidermotropism. Spongiosis should not be present. If spongiosis is present, then a different diagnosis should be considered. Pautrier's microabscesses and TCR rearrangements are variably present and not essential for the diagnosis of MF.
7. B. This lymph node does not qualify as an abnormal lymph node; therefore, it does not meet the criteria for biopsy. An abnormal lymph node is defined as > 1.5 cm in its longest transverse diameter or with abnormal palpable qualities (firm, irregular, fixed, clustered). Skin biopsy is necessary for initial diagnosis. Bone marrow biopsy is merited in patients with high blood tumor burden (B2) and in those with an unexplained hematologic abnormality. HIV and HTLV are checked as they are the etiologies of other non-MF/SS CTCLs.
8. C. He now has a clinically significant lymph node which may be positive for MF. Many would also order a repeat CT or PET/CT scan to detect other lymphadenopathy as well as a flow cytometry to see if this increased aggressiveness in the skin is also manifested in the blood. It would be premature to reassign to stage IIB (D) as his lymph node pathology grade could make him stage IVA2. Bone marrow biopsy (A) is not merited unless the re-staging flow cytometry shows B2 blood involvement. Once the full re-staging work-up is complete, the stage is reassigned. Changing therapies (B) is necessary but dependent on confirmation of these new findings. Therefore changing therapies is secondary to the re-staging workup and not the *next* step. Continuing to monitor (E) can only result in more aggressive disease as his current regimen is not sufficient.
9. A. IIIA describes erythroderma without any blood involvement. If the patient also had low blood tumor burden, they would be IIIB. If they had high tumor burden they would be IVA1. Since the patient does not have any lymph nodes or organs involved, he/she does not qualify for stage IVA2 or IVB, respectively.
10. B. ECP in combination with interferon and bexarotene is most commonly used for SS patients. Alemtuzumab (A) is also emerging as a secondary agent for SS but is immunosuppressive. The other treatments (C, D, E) are less effective as they are skin-directed therapies, and SS is a leukemic variant.

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VASCULAR TUMORS AND MALFORMATIONS

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OVERVIEW

- Vascular tumors: dynamic lesions that clinically demonstrate proliferation and are characterized histologically by endothelial cell hyperplasia: epidermis appears atrophic, few vellus hair follicles, no subcutaneous fat
- Vascular tumors of infancy and childhood
 - Infantile hemangioma
 - “Congenital hemangiomas” (noninvoluting, or NICH; rapidly involuting, or RICH)
 - Kaposiform hemangioendothelioma
 - Tufted angioma
 - Pyogenic granuloma
 - Endovascular papillary angioendothelioma (Dabska tumor)
- Vascular tumors of adulthood
 - Kaposi sarcoma
 - Angiolymphoid hyperplasia with eosinophilia
 - Intravascular papillary endothelial hyperplasia (Masson’s tumor)
 - Low-grade angiosarcomas
 - Epithelioid hemangioendothelioma
 - Spindle cell hemangioendothelioma
 - Retiform hemangioendothelioma
 - Angiosarcoma
- Vascular malformations
 - Almost always present at birth (although they may not manifest until later in childhood)
 - Arise from dysmorphogenesis
 - Exhibit normal cellular turnover
 - Are static or undergo slow expansion over time
- Can be further subdivided on the basis of
 - Flow rate
 - ▲ Slow flow: capillary, venous, or lymphatic
 - ▲ Fast flow: arteriovenous fistulas and arteriovenous malformations
 - Resemblance to vessel type: capillary, lymphatic, venous, or arteriovenous; can occur alone or in combination
 - ▲ Capillary
 - △ Salmon patch
 - △ Port wine stain
 - △ Phakomatosis pigmentovascularis
 - △ Telangiectasia
 - △ Cutis marmorata telangiectatica congenita
 - △ Unilateral nevoid telangiectasia
 - △ Angiokeratomas
 - ▲ Lymphatic: microcystic, macrocystic, or combined
 - ▲ Venous
 - △ Blue rubber bleb nevus syndrome
 - △ Glomuvenous malformations: glomus tumors, glomangiomas, and glomangiomatosis
 - ▲ Arterial
 - △ Arteriovenous fistula
 - △ Arteriovenous malformation
 - ▲ Combined
 - △ Klippel-Trenaunay syndrome (capillary-lymphaticovenous malformation)

- △ Parkes-Weber syndrome (capillary-arteriovenous fistula and capillary-arteriovenous malformation)

VASCULAR TUMORS OF INFANCY AND CHILDHOOD

Infantile Hemangioma (IH)

- Characteristics
 - Most common tumor of infancy
 - Characterized by endothelial cell proliferation
 - GLUT-1 (glucose transporter) is an immunohistochemical stain specific for IH in all phases of growth and involution
 - Positive staining occurs *only* with IH and *not* with any other vascular tumor or malformation
 - Proliferative phase: 6 to 12 months; rarely longer
 - Involution phase: gradual over several or more years
 - Risk factors: Caucasian, female, low birth weight, multiple gestation
- Location: more than 60% occur on head or neck, most commonly midcheek, lateral upper lip, and upper eyelid
- Types
 - Superficial, deep, or combined
 - Superficial
 - ▲ Most common
 - ▲ Raised, bright-red papule, nodule or plaque
 - Deep: soft, flesh-colored nodule that often has a bluish hue and/or central telangiectasias
 - Combined (Fig. 13-1)
 - Localized, segmental, or multiple
- Classification by morphology
 - Localized: papules or nodules that appear to arise from a single focal point and demonstrate clear spatial containment
 - Segmental (Fig. 13-2)
 - Plaque-like and show a linear and/or geographic pattern over a cutaneous territory
 - Much more likely to be complicated, require more intensive and prolonged therapy, and have a poorer overall outcome
 - Multifocal
 - Generally defined as five or more small, localized lesions
 - Multiple hemangiomas are associated with multiple births
- Complications
 - Ulceration
 - Most common in proliferative phase
 - Often leads to pain, scarring, bleeding, secondary infection
 - Favors IH in trauma-prone sites: lip, perineum, intertriginous, posterior scalp, back
 - Scarring
 - More common with segmental IH, localized IH of superficial, raised morphology with sharp “cliff drop” border, ulceration
 - High-risk locations: lip (especially when crossing the vermillion border), nasal tip, ear
 - Vital organ compromise
 - Visual obstruction



FIGURE 13-1 Combined infantile hemangioma. (Courtesy of Dr. Denise Metry.)



FIGURE 13-2 Segmental facial infantile hemangioma. (Courtesy of Dr. Denise Metry.)

- ▲ Amblyopia from stimulus deprivation or astigmatism
- ▲ Most common when IH involves upper eyelid (Fig. 13-3)
- ▲ Refer to ophthalmology
- Airway (especially subglottic) IH
 - ▲ Associated with segmental IH in a cervicofacial or “beard” distribution
 - ▲ Watch for development of stridor
 - ▲ Endoscopy for definitive diagnosis
- Visceral IH
 - Associated with multifocal *and* solitary segmental IH
 - Liver most worrisome site
 - Severe hypothyroidism may result from the inactivation of thyroid hormone by type 3 iodothyronine deiodinase in the hemangioma
 - Gastrointestinal IH can lead to significant bleeding
 - Brain involvement can lead to mass effects/neurologic sequelae
- Lumbosacral IH
 - Segmental lesions that span the midline and often are flat or telangiectatic in appearance are at highest risk
 - Risks: spinal dysraphism (especially tethered cord; supragluteal cleft deviation is an especially concerning clinical sign), anorectal anomalies, bony anomalies of the sacrum, abnormal genitalia, renal abnormalities, lipomeningomyelocele
- MRI best study for spinal dysraphism
- Developmental anomalies
 - PHACE syndrome
 - ▲ Posterior fossa (Dandy-Walker) brain malformations, hemangioma (segmental, usually cervicofacial), cerebrovascular arterial anomalies, cardiac defects/coarctation of the aorta, eye anomalies
 - ▲ Sometimes referred to as PHACE(S) when ventral developmental defects such as sternal clefting and supraumbilical raphe are present
 - ▲ Structural cerebral and cerebrovascular anomalies: most common and potentially serious manifestations
 - ▲ Cerebrovascular anomalies can lead to progressive vasculopathies causing stroke in early childhood
 - ▲ Workup
 - △ MRI/MRA of brain and neck
 - △ Cardiac echo or MRI/MRA of chest
 - △ Eye examination
- Diagnosis
 - Generally clinical
 - Surgical biopsy (\pm GLUT-1 staining) warranted if any suspicion for malignancy
 - Imaging studies cannot generally be relied on to distinguish a benign from malignant vascular tumor
- Treatment
 - Most common indications: ulceration, vital organ compromise, to improve the ultimate cosmetic outcome
 - Options
 - Meticulous wound care for ulceration
 - Corticosteroids: topical, intralesional, or systemic
 - ▲ Second-line agents
 - △ Vincristine
 - △ Interferon (20% risk of spastic diplegia in infants)
 - △ Excisional or laser surgery in select patients



FIGURE 13-3 Segmental hemangioma. (Courtesy of Dr. Denise Metry.)

“Congenital” Hemangiomas

- Types: noninvoluting (NICH), rapidly involuting (RICH)
 - Uncommon
 - Fully developed at birth and GLUT-1-negative
- RICH
 - Gray-violaceous tumor
 - Most common on an extremity
 - Undergoes rapid involution during the first year of life with characteristic atrophy

- NICH
 - Most commonly presents on the trunk
 - Oval to round plaque with coarse, central telangiectasias and a surrounding rim of pallor
 - Often feels warm to palpation and may have a slight bruit
 - Path is hybrid between a vascular tumor and malformation

Kaposiform Hemangioendothelioma

- Characteristics
 - Rare
 - Histologically benign but clinically aggressive tumor
 - Most commonly affects children younger than 2 years of age and is often present at birth
 - Male-female incidence equal
 - Generally solitary
 - Favors the skin (particularly trunk, extremities) or retroperitoneum
 - Grows rapidly
 - Early on develops distinct violaceous color as a clue to underlying Kasabach-Merritt phenomenon (KMP)
 - KMP = life-threatening thrombocytopenia as a result of platelet trapping within the tumor
 - Consumption coagulopathy with very low platelet counts and low fibrinogen levels
 - Does not occur with IH
- Pathology: densely infiltrated nodules composed of spindle cells with minimal atypia and infrequent mitoses and slit like vessels containing hemosiderin; GLUT-1-negative
- Treatment
 - Corticosteroids often used as first-line therapy but rarely effective alone
 - Complete surgical excision if feasible
 - Interferon- α , vincristine
 - Platelets and heparin should be avoided

Tufted Angioma (Angioblastoma of Nakagawa) (Fig. 13-4)

- Characteristics
 - Uncommon, histologically benign tumor
 - Presents during infancy or early childhood; presence at birth uncommon
 - Most common on trunk, extremities
 - Slow, lateral extension occurs over months to years
 - Spontaneous regression may occur, though rarely
 - Variable presentation
 - Large, erythematous plaque with cobblestone surface
 - Sometimes with overlying vellus hair growth, tenderness, sweating



FIGURE 13-4 Tufted angioma. (Courtesy of Dr. Denise Metry.)



FIGURE 13-5 Pyogenic granuloma. (Courtesy of Dr. Denise Metry.)

- Associated with KMP less commonly than kaposiform hemangioendothelioma
- Histology: tufts of capillaries throughout dermis, “cannonball” pattern

Pyogenic Granuloma (Fig. 13-5)

- Characteristics
 - Can be seen at any age, but majority occur during childhood
 - Prior history of trauma in minority
 - Most common on head and neck; mucosal lesions more common in females, especially during pregnancy
 - Usually presents as rapidly growing, bright-red papule or nodule
 - Bleeds repeatedly and profusely; generally does not regress

- Umbilical granulomas seen in neonates have similar clinical appearance, but if persistent, may represent umbilical remnant (imaging recommended)
- Histology: well-circumscribed lobular proliferation of capillaries; possible erosion of epidermis
- Treatment
 - Depends on location/size
 - Most small lesions can be shave excised or curetted with light electrodesiccation to the base
 - Alternatives: excision, pulsed-dye or carbon dioxide laser, cryotherapy
- Course: recurrence more common with larger lesions

VASCULAR TUMORS OF ADULthood

Kaposi Sarcoma (KS)

- Associated with human herpesvirus type 8
- Subtypes
 - Classic KS
 - Males, older than 50 years of age, predominant in Mediterranean and Jewish populations
 - Increased risk of lymphoreticular neoplasms
 - Violaceous macules with slow progression to plaques
 - Distal lower extremities, unilateral involvement with centripetal spread to a disseminated and multifocal pattern
 - Oral cavity and GI tract (90%); possible involvement of lung, spleen, and heart
 - Benign course owing to slow progression
 - African endemic KS
 - Black Africans, males > females, third to fourth decades
 - In children, the disease runs a fulminant course with rapid dissemination
 - Clinicopathologic subvariants
 - ▲ Nodular: benign, similar to classic KS
 - ▲ Florid or vegetating type: nodules extend into deep dermis, subcutis, muscle, and bone
 - ▲ Infiltrative: like florid/vegetating type but more aggressive
 - ▲ Lymphadenopathic: affects children and young adults, usually confined to lymph nodes but may affect skin and mucous membranes
- KS in iatrogenically immunocompromised patients
 - Presents in organ-transplant, autoimmune, and cancer patients
 - Discontinuation of therapy may cause regression of KS lesions
- Epidemic HIV-associated KS

- Oral mucosa (palate most common) is initial site of presentation in 10% to 15%
- Early lesions appear as small pink/reddish macules or dermatofibroma-like papules
- Extracutaneous sites: lymph nodes, gastrointestinal tract (80% of AIDS patients, usually duodenum and stomach), and lungs (bronchospasm, cough, respiratory insufficiency)
- Histology
 - Patch stage: proliferation of spindle-shaped cells in upper dermis; neoplastic cells outline irregular, bizarre slits and clefts
 - Plaque stage: multiple dilated and angulated vascular spaces outlined by attenuated endothelium, solid cords, and fascicles of spindle cell arranged between jagged vascular channels
 - Tumor stage: spindle cells in interlacing fascicles in dermis; lack of pronounced pleomorphism and nuclear atypia, slit like vascular spaces with extravasated red blood cells (RBCs)
- Treatment
 - Ionizing radiation
 - (Poly) chemotherapy: vinblastin or vincristin; combination with actinomycin D, adriamycin, bleomycin, and dacarbazine; liposomal encapsulated doxorubicin and daunorubicin
 - Interferon- α in combination with antiretrovirals (zidovudine)
 - Topical tretinoin gel
 - Topical imiquimod
 - Intralesional injections of β -human chorionic gonadotropin (β -hCG)

Angiolymphoid Hyperplasia with Eosinophilia

- Characteristics
 - Occurs mainly in the West
 - Thought to be inflammatory or reactive process
- Location: head, trunk, extremities
- Presentation
 - Peripheral eosinophilia
 - Papules or nodules
 - Young adults, females > males
- Diagnosis/pathology
 - Irregular vessels lined by plump endothelial cells with “hobnail” appearance
 - Infiltrate of lymphocytes, histiocytes, and eosinophils

Kimura's Disease

- Characteristics
 - Occurs mainly in Asia
 - Classified as cutaneous lymphoid hyperplasia
- Location: head
- Presentation
 - Solitary or multiple nodules

- Young to middle-aged adults
- Almost exclusively male
- Peripheral eosinophilia and lymphadenopathy
- Diagnosis/pathology
 - Hyperplasia of small vessels lined with plump endothelial cells within the dermis or subcutis
 - Dense infiltrates of lymphocytes, plasma cells, histiocytes, and eosinophils
 - Multiple lymphoid follicles with germinal centers

Intravascular Papillary Endothelial Hyperplasia (Masson's Pseudoangiosarcoma)

- Characteristics
 - Reactive hyperplasia after intravascular thrombosis
 - As a focal change in a preexisting vascular lesion (hemangioma, pyogenic granuloma, or vascular malformation)
 - Small (< 2 cm in diameter), firm, blue or purple nodule
 - Located on extremities, usually fingers
- Histology
 - Papillated vascular structures extending from the wall within vascular lumina are lined by single layer of plump endothelial cells
 - Occluded by thrombus
- Treatment: simple excision

Low-Grade Angiosarcoma

- Types
 - Endovascular papillary angioendothelioma (Dabska tumor)
 - Epithelioid hemangioendothelioma
 - Retiform hemangioendothelioma
- Location
 - Skin or soft tissue of extremities
 - Extremities > scalp
- Presentation
 - Solitary tender nodule
 - Plaques and nodules
- Complications
 - Frequent recurrence but low metastatic rate
 - Greater than 50% with metastasis die of disease

Dabska Tumor (Papillary Intralymphatic Angioendothelioma)

- Characteristics
 - Low-grade angiosarcoma that affects the skin of children
 - Slow-growing, painless, intradermal nodule that grows to 2 to 3 cm
- Laboratory studies
 - Immunoreactivity for factor VIII-related antigen, *Ulex europaeus* agglutinin I, vimentin, blood group isoantigens, and C2.1 antibody

- Histology
 - Multiple vascular channels that interconnect
 - Lined by atypical endothelial cells; vacuolated cytoplasm, and hyperchromatic eccentric nuclei
 - Weibel-Palade bodies may be present
- Treatment: wide local excision is the treatment of choice; regional lymph node dissection if clinically necessary
- Prognosis: favorable prognosis; however, they can be locally invasive and have the potential to metastasize

Hemangioendothelioma (Epithelioid and Spindle)

- Characteristics
 - Poorly circumscribed, usually biphasic proliferation of venous or capillary vessels
 - Minimal dysplasia, few mitotic figures, and minimal differentiation toward a vascular lumen or channel
 - A third of epithelioid hemangioendotheliomas develop metastases in regional lymph nodes
 - Red/blue nodules that may be multiple and are usually superficial
 - Distal extremities (particularly the hands)
 - Second and third decades of life
- Types
 - Epithelioid hemangioendothelioma: vessels are intermixed with solid sheets of epithelioid cells
 - Spindle cell hemangioendothelioma: spindle-shaped mesenchymal cells; this can occur at any age; thought to represent a reactive vascular tumor arising in conjunction with malformed vasculature (primarily lymphatic); can be associated with Maffucci's syndrome
- Histology: slit like vascular channels, mild extravasation of erythrocytes, and hemosiderin deposition; epithelioid cells have abundant eosinophilic cytoplasm; spindle cell variant has bland bipolar mesenchymal fibroblast-like cells that may contain vacuoles that stain with *Ulex europaeus* and cytoplasmic factor VIII-associated antigen
- Treatment
 - Wide surgical excision
 - Greater than 50% of cases recur at the operative site or several centimeters distant

Retiform Hemangioendothelioma

- Characteristics
 - Slowly growing exophytic or plaque like tumor is usually noted in young adults, predominantly on the lower limbs
 - May be associated with radiotherapy or chronic lymphedema
- Histology: arborizing vessels; focal solid areas composed of spindle and epithelioid; vessels lined by



FIGURE 13-6 Angiosarcoma. (Courtesy of Dr. Adelaide Hebert.)

“hobnail” endothelial cells, prominent stromal lymphocytic infiltrate

Angiosarcoma (Fig. 13-6)

- Characteristics: subtypes
 - Idiopathic angiosarcoma
 - Elderly patients
 - Purpuric macule, plaque, nodule, or ulceration
 - Location: scalp, upper forehead
 - Lymphedema-associated angiosarcoma
 - Edematous arm of women after mastectomy on side with lymphadenectomy (Stewart-Treves syndrome)
 - Bluish plaques, nodules, and vesicles
 - Post irradiation angiosarcoma: years after radiotherapy
- Diagnosis
 - Histology
 - Irregular anastomosing vascular channels
 - Lined by hyperchromatic, pleomorphic endothelial cells; mitosis prominent
 - Immunohistochemistry: CD31, CD34, and factor VIII-related antigen are less specific

VASCULAR MALFORMATIONS

Capillary

SALMON PATCH (NEVUS SIMPLEX) (FIG. 13-7)

- Characteristics
 - Best classified as capillary malformation
 - Prognosis generally differs from port-wine stain
 - Thought to represent persistent fetal circulatory patterns in the skin



FIGURE 13-7 Nevus simplex. (Courtesy of Dr. Denise Metry.)

- Disappears when the autonomic innervation of these vessels matures during infancy
- Present in nearly half of all newborns
- Slow flow
- Location: nape of neck > eyelid > glabella (“angel’s kiss”) > nasolabial region
- Presentation
 - Pink to red patch
 - Usually fades by 1 to 2 years of age, although lesions of the nape persist

PORT-WINE STAIN (NEVUS FLAMMEUS) (FIG. 13-8)

- Characteristics
 - Capillary malformation
 - Slow flow
- Location: variable
- Presentation
 - Present at birth as erythematous patch
 - Persists throughout life
 - With age (predominantly with facial lesions), can develop a dark red or deep purple color with nodules and/or pyogenic granuloma like lesions
- Complications/associations
 - Bony and soft tissue hypertrophy, especially in the V2 and V3 facial distributions
 - Sturge-Weber syndrome (encephalotrigeminal angiomatosis)
 - Triad
 - Facial port-wine stain
 - ▲ Usually trigeminal V1 dermatome: forehead and upper eyelid
 - ▲ Approximately 10% of infants with port-wine stain in trigeminal V1 location will have Sturge-Weber syndrome



FIGURE 13-8 Port-wine stain. (Reprinted with permission from Wolff et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- Ipsilateral ocular vascular anomalies: can lead to retinal detachment, glaucoma, and blindness
- Leptomeningeal vascular anomalies: can lead to early-onset seizures
- Midline facial stains have been associated with Beckwith-Wiedemann syndrome
- Diagnosis/pathology: dilated, mature capillaries in the superficial dermis
- Treatment
 - Flashlamp-pumped, pulsed-dye laser (585 and 595 nm)
 - Low risk of scarring
 - Multiple treatments required
 - Most patients achieve lightening but not complete clearance
 - V2 and distal extremity lesions less responsive
 - Cosmetic camouflage

PHAKOMATOSIS PIGMENTOVASCULARIS

- Characteristics
 - Coexistence of capillary malformation with a melanocytic or epidermal lesion (dermal melanocytosis, nevus spilus or speckled lentiginous nevus, nevus anemicus)



FIGURE 13-9 Cutis marmorata telangiectatica congenita. (Reprinted with permission from Wolff et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- Hereditary disorder thought to be explained by the “twin spot” phenomenon

CUTIS MARMORATA TELANGIECTATICA CONGENITA (FIG. 13-9)

- Characteristics
 - Congenital, with reticulate purple network
 - Most cases occur sporadically
 - May be associated with atrophy and/or ulceration
 - Limb + / – trunk
 - Limb girth discrepancy: common; other associated anomalies probably less common
- Diagnosis: generally clinical
- Treatment: no treatment is needed unless associated anomalies
- Erythema improves over time

UNILATERAL NEVOID TELANGIECTASIA (UNT)

- Characteristics
 - Congenital or acquired patches of superficial telangiectases in a unilateral linear distribution
 - May result from a somatic mutation during embryologic development
 - Third and fourth cervical dermatomes most common sites, thoracic dermatomes or scattered distant sites also may be involved
 - Pathogenesis of UNT remains unknown, possibly related to hormonal causes
- Histology: dilated capillaries in the superficial dermis
- Treatment: pulsed-dye lasers

ANGIOKERATOMA

- Characteristics
 - Slow flow
 - Capillary ectasia in the papillary dermis
 - May produce papillomatosis, acanthosis, and hyperkeratosis of the epidermis
 - Types
 - Angiokeratomas of Fordyce
 - Uncommon
 - 2- to 4-mm red-to-blue domed papules with keratotic surface
 - Peak incidence after the third decade; more common in males
 - Most often on the scrotum and vulva
 - Lesions number from one to many (> 100)
 - Angiokeratoma circumscriptum
 - Uncommon
 - Small red macules coalesce to form large acanthokeratotic plaques
 - Usually occurs in childhood; equally common in males and females
 - Often found on the extremities
 - Associated with vascular malformations and atrophy or hypertrophy of regional soft tissue and bone
 - Angiokeratoma corporis diffusum (Fabry's disease)
 - Rare
 - X-linked inherited disorder
 - Caused by a deficiency of the lysosomal enzyme α -galactosidase
 - Unremitting deposition of neural glycosphingolipids in the lysosomes of: vascular endothelium, fibroblasts, and pericytes of the dermis, heart, kidneys, and autonomic nervous system
 - Clinical findings:
 - ▲ Skin: verrucous papules, deep red to blue-black in color, between the umbilicus and the knees, with a predilection for the scrotum, penis, lower back, thighs, hips, buttocks
 - ▲ Ocular: corneal opacities, posterior capsular cataracts
 - ▲ Neurologic: burning, tingling paresthesias, hemiplegia, hemianesthesia, balance disorders, and personality changes
 - ▲ Extremities: chronic edema of the feet, arthritis of the distal interphalangeal joints
 - ▲ Cardiac: infiltration results in angina, myocardial infarction, mitral valve prolapse, congestive heart failure, hypertension, mitral insufficiency, and ventricular hypertrophy
 - ▲ Urinalysis: urinary maltese crosses of lipid globules
 - Angiokeratoma of Mibelli
 - Uncommon
 - Multiple 3- to 5-mm dark red papules with verrucous surface
 - Most often affects females younger than 20 years
 - Most often found on dorsa of fingers and toes; less commonly observed on elbows, knees, shoulders, and earlobes
 - Associated with recurrent chilblains and acrocyanosis
 - Autosomal dominant inheritance with variable penetrance
 - Solitary angiokeratoma (Fig. 13-10)
 - Most common type
 - 2- to 10-mm dark papules or plaques that keratinize and turn blue-black
 - Peak incidence during third to fourth decades of life; more common in males
 - Presents most often on the lower extremities
- Treatment
 - Either ablation or excision can be performed
 - Erbium or carbon dioxide laser to remove the hyperkeratotic-acanthotic epidermis, followed by the use of lasers that target hemoglobin
 - Cryotherapy

Lymphatic Malformation (Fig. 13-11)

- Characteristics
 - Slow flow
 - Microcystic (lymphangioma circumscriptum, lymphangioma)
 - Macrocystic (cystic hygroma)
 - Combined
- Location
 - Macrocystic
 - Neck, axilla, groin, or chest wall



FIGURE 13-10 Solitary angiokeratoma. (Courtesy of Dr. John Browning.)



FIGURE 13-11 Lymphatic malformation. (Reprinted with permission from Wolff et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- Large lesions documented on fetal ultrasound may be associated with Down or Turner syndrome
- Microcystic: axillary folds, shoulders, neck, proximal limbs, perineum, tongue, floor of mouth
- Presentation
 - May become evident at birth or become so in early childhood
 - Microcystic lymphangiomas of the skin
 - Consist of grouped, clear vesicles (“frog spawn”)
 - May contain blood, giving lesions a pink, purple, or black color
 - May have overlying hyperkeratosis
- Complications/associations: numerous, depending on location, but disfigurement, infection, bleeding most common
- Diagnosis
 - Histology
 - Ectatic thin-walled channels filled with lightly eosinophilic lymph
 - Lymphatic endothelial marker: D2-40
 - MRI: best means of determining lesion extent
- Treatment
 - Surgery and/or sclerotherapy: mainstay of therapy, although cure rarely achieved except with small, well-localized lesions
 - OK-432
 - Killed strain of group A *Streptococcus pyogenes*

- Additional sclerotherapeutic agent useful for macrocystic lesions
- Laser photocoagulation: can be temporizing measure for microcystic cutaneous lesions
- Elastic compression stockings for extremity lesions

VENOUS MALFORMATION: GENERAL

- Characteristics: slow flow
- Location: skin, subcutaneous tissues, mucosa
- Presentation
 - Present, though not always evident, at birth
 - Usually solitary, localized
 - Soft, deep-blue masses that are easily compressible and slowly refill on release
 - Swell with dependency or activity
 - Undergo slow expansion over time
 - Phleboliths (progressive calcifications) are a hallmark of venous malformation and a common source of localized pain
 - Pain and stiffness on morning awakening and dull aching are other common complaints
- Associated conditions
 - Blue-rubber bleb nevus syndrome: autosomal dominant
 - Clinical
 - ▲ Skin (most commonly trunk, palms and soles) and bowel venous malformations
 - ▲ Latter commonly leads to chronic gastrointestinal bleeding
 - Diagnosis
 - ▲ Histology: anomalous, dilated veins with irregularly thickened walls
 - ▲ MRI best means of determining lesion extent
 - Treatment
 - ▲ Elastic support stockings of affected extremity
 - ▲ Low-dose aspirin may be useful for painful thrombosis
 - ▲ Sclerotherapy and/or surgery reserved for lesions causing significant functional compromise or cosmetic deformity
- Glomuvenous malformations: also known as glomus tumors, glomangiomas, or glomangiomas (Fig. 13-12)
 - Characteristics
 - ▲ Solitary tumors most common in adults, sporadically inherited
 - ▲ Multiple more common in childhood and generally autosomal dominant (linked to chromosome 1p21-22)
 - ▲ Solitary, extremely tender lesions most common on upper extremities, especially in nail beds

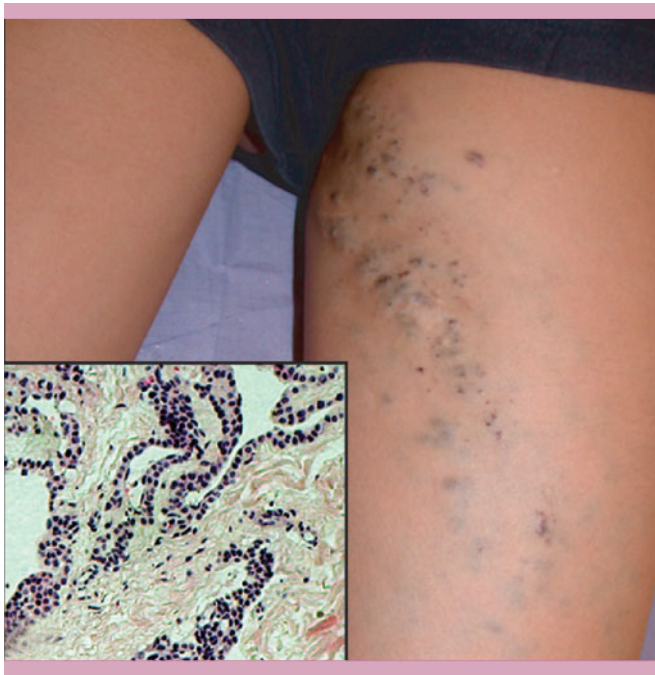


FIGURE 13-12 Superficial glomuvenous malformation on the thigh; note presence of mural glomus cells on H&E stained histologic sample. (Reprinted with permission from Wolff et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- ▲ Multiple lesions may be scattered or grouped, often in a segmental distribution
- ▲ Congenital lesions tend to be large and plaque like and are bluish purple with a “cobblestone” and/or hyperkeratotic appearance
- ▲ Resemble venous malformation but lack tendency toward mucosal or deep muscle involvement, are firmer and less compressible, and frequently tender to palpation
- Histology: shows overlapping features of capillary-venous malformation and glomus cell tumor
- Treatment: surgical excision only reliable treatment

Arteriovenous Malformation

- Characteristics: fast flow, the most dangerous type of vascular anomaly
- Presentation
 - Present at birth but may manifest later.
 - Early lesions may appear as a faint vascular stain that is often mistaken for a capillary malformation
 - Will eventually manifest itself, often following trauma or with the onset of puberty, as a warm, pulsatile mass with draining veins and deepening of color

- End stage lesion: ulceration, bleeding, intractable pain, disfigurement
- Location: intracranial > extremities > trunk > viscera
- Treatment
 - Always complex and difficult
 - Generally should not be considered until significant symptoms develop
 - Embolization
 - Surgery

Maffucci Syndrome

- Inheritance: sporadic
- Clinical
 - Triad of chondrodysplasia of one or more limbs, multiple enchondromas, and vascular lesions
 - Vascular lesions include venous malformations and spindle cell hemangioendotheliomas
 - Enchondromas, exostoses, recurrent fractures
 - Neurologic deficits result from cerebral enchondromas.
 - Risk of chondrosarcoma (15% to 20%), angiosarcoma, fibrosarcoma, osteosarcoma, lymphangiosarcoma, intracranial tumors

Cobb Syndrome (Cutaneomeningospinal Angiomatosis)

- Inheritance: sporadic
- Clinical
 - Arteriovenous malformation (AVM) of the spinal cord with overlying cutaneous “blush” of the posterior thorax
 - Neurologic problems secondary to cord compression by the AVM or spinal subarachnoid hemorrhage
 - May result in pain, subarachnoid hemorrhage, motor or sensory deficit
- Treatment: see AVM

Complex Vascular Malformation Syndromes

KLIPPEL-TRENAUNAY-WEBER SYNDROME

- Inheritance
 - Sporadic, males > females
 - Most common vascular malformation syndrome
- Clinical
 - Triad of port-wine stain, venous and/or lymphatic malformation, and bony and/or soft tissue hypertrophy
 - Typically limited to a single extremity
 - Lymphatic component common, evidenced by lymphedema or cutaneous lymphatic vessels
 - Overgrowth of affected limb apparent at birth or occurs within the first few months to years of life
- Treatment
 - Compression hose

- Regular visits to clinically and radiographically assess for limb length discrepancy; if significant, refer to orthopedics
- See VM, LM, CM

PROTEUS SYNDROME

- Inheritance: sporadic
- Clinical
 - Disproportionate overgrowth of multiple tissues in association with various cutaneous and subcutaneous mesodermal hamartomas, including vascular malformations
 - Changes can be present at birth or develop over time
 - Striking cerebriiform hyperplasia of the plantar feet
 - Associated with mutations in PTEN tumor-suppressor gene

BECKWITH-WIEDEMANN SYNDROME

- EMG (exomphalos-macroglossia-gigantism) syndrome
- Capillary malformation at midforehead
- Inheritance: sporadic
- Clinical
 - Macroglossia
 - Exomphalos
 - Linear earlobe creases; circular depression on helix
 - Gigantism
 - Organomegaly (big baby, big tongue, big organs)
 - Wilm's tumor, adrenal cortical carcinoma, rhabdomyosarcoma, hepatoblastoma
 - Omphalocele; intestinal malrotation

QUIZ

Questions

- Which immunohistochemical stain is specific to infantile hemangioma?
 - aGLUT-1
 - Ulex europaeus* agglutinin 1
 - Vimentin
 - Factor VIII-related antigen
 - Endothelin-1 antibody
- Other than the facial hemangioma, the most common features of PHACE are:
 - Structural and cerebrovascular anomalies of the brain
 - Ocular anomalies
 - Cardiovascular anomalies
 - Ventral developmental defects
- PHACE patients with cerebrovascular anomalies are most at risk for which of the following complications during infancy?
 - Motor developmental delay
 - Language developmental delay
 - Acute arterial ischemic stroke
 - Migraine-like headaches
- The Kasabach-Merritt phenomenon may be seen with:
 - Infantile hemangioma (IH)
 - Rapidly involuting congenital hemangioma (RICH)
 - Non-involuting congenital hemangioma (NICH)
 - Kaposiform hemangioendothelioma
 - All the above
- A 2-month-old female presents with a large segmental hemangioma of the face; all of the following studies are indicated EXCEPT:
 - MRI/MRA of the head and neck
 - Echocardiogram
 - Renal ultrasound
 - MRI of the heart
 - All of the above are indicated
- The following are subtypes of Kaposi sarcoma (KS), EXCEPT:
 - African endemic KS
 - Classic KS
 - Epidemic HIV-associated KS
 - Asian endemic KS
 - All of the above are subtypes
- All of the following statements regarding classic Kaposi sarcoma are true, EXCEPT:
 - It is more common in men than women
 - Involvement of the upper extremities is more common than the lower extremities
 - Ionizing radiation may be used as a form of treatment
 - Topical imiquimod may slow progression of the disease
 - The lungs, spleen, and heart may be involved
- Upon histologic examination of a vascular neoplasm, tufts of capillaries in a cannonball pattern are seen throughout the dermis. What is the most likely diagnosis?
 - Kaposi sarcoma
 - Pyogenic granuloma
 - Tufted angioma
 - Infantile hemangioma
 - Kimura's disease

9. Which of the following statements best describes Dabska tumor?
 - A. A rare, low-grade angiosarcoma that often affects the skin of children
 - B. Reactive hyperplasia after intravascular thrombosis
 - C. An exophytic tumor in young adults, predominantly located on the lower extremities
 - D. A vascular tumor present at birth that undergoes rapid involution
 - E. A violaceous tumor associated with thrombocytopenia
10. Rapid involuting hemangioma (RICH) can be distinguished from non-involuting congenital hemangioma (NICH) by all of the following EXCEPT:
 - A. Clinical course
 - B. Location on the body
 - C. Color
 - D. GLUT-1 staining
 - E. Presence of a bruit

Answers

1. Infantile hemangioma is positive for GLUT-1, a stain which is also positive in placental tissue.
2. A. PHACE stands for **P**osterior fossa (Dandy-Walker) brain malformations, **H**emangioma (segmental, usually cervicofacial), cerebrovascular **A**rterial anomalies, **C**ardiac defects/coarctation of the aorta, **E**ye anomalies. Structural cerebral and cerebrovascular anomalies are the most common and potentially serious manifestations.
3. C. Structural cerebral and cerebrovascular anomalies are the most common and potentially serious manifestations in PHACE patients. Cerebrovascular anomalies can lead to progressive vasculopathies causing stroke in early childhood.
4. D. Patients with kaposiform hemangioendothelioma are at risk of developing Kassabach-Merritt phenomenon (KMP), a life-threatening thrombocytopenia as a result of platelet trapping within the tumor. KMP is a consumption coagulopathy with very low platelet counts and low fibrinogen levels. KMP does not occur with IH.
5. C. A patient with a large segmental hemangioma of the face is at risk of having PHACE syndrome. PHACE stands for **P**osterior fossa (Dandy-Walker) brain malformations, **H**emangioma (segmental, usually cervicofacial), cerebrovascular **A**rterial anomalies, **C**ardiac defects/coarctation of the aorta, **E**ye anomalies. Renal anomalies are not part of PHACE syndrome.
6. D. African endemic KS, classic KS, and epidemic HIV-associated KS are all subtypes of KS. Asian endemic KS is not a distinct KS subtype.
7. B. Classic KS typically affects males older than 50 years of age, predominant in Mediterranean and Jewish populations. These patients have increased risk of lymphoreticular neoplasms. Clinically, classic KS appears as violaceous macules with slow progression to plaques. It involves the distal lower extremities, with unilateral involvement and centripetal spread to a disseminated and multifocal pattern. The oral cavity and GI tract (90%) are commonly affected; possible involvement of lung, spleen, and heart. Classic KS has a benign course owing to slow progression.
8. C. Histologic examination of tufted angioma shows tufts of capillaries throughout dermis in a “cannonball” pattern.
9. A. Dabska tumor is a low-grade angiosarcoma that affects the skin of children. It is a slow-growing, painless, intradermal nodule. Dabska tumor has immunoreactivity for factor VIII-related antigen, Ulex europaeus agglutinin I, vimentin, blood group isoantigens, and C2.1 antibody. Histologically, multiple vascular channels that interconnect are lined by atypical endothelial cells; vacuolated cytoplasm, and hyperchromatic eccentric nuclei. Weibel-Palade bodies may be present. Wide local excision is the treatment of choice; regional lymph node dissection if clinically necessary. Prognosis is favorable; however, the tumor can be locally invasive and has the potential to metastasize.
10. D. Only infantile hemangioma is GLUT-1 positive.

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GENODERMATOSIS

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EPIDERMOLYSIS BULLOSA

- Disorder with the formation of bullae and erosions following mechanical trauma to the skin and mucosa.
- Gene defects cause abnormalities in structural proteins of the epidermis and the epidermal-dermal junction.
- Subtypes are classified based on the ultrastructural level of blisters (Table 14-1), mode of inheritance, and the clinical features.
- There are four major EB types (Table 14-2) and multiple related subtypes (Table 14-3).

Diagnosis:

- Transmission electron microscopy (EM): evaluation of level of skin cleavage: intraepidermal, intra-lamina lucida, or sub-lamina densa
- Immunofluorescence mapping (IFM): monoclonal antibodies, can identify the structural protein most likely mutated resulting in the different forms of EB. (Table 14-4)
- Mutational analysis: determines the mode of inheritance and the precise site(s) and type(s) of molecular mutation present. (Table 14-5)

Epidermolysis Bullosa Simplex (EBS)

- Autosomal dominant (most common) or recessive
 - Targeted proteins include: keratins 5 and 14 (encode basal cell keratin), desmoplakin, plakophilin-1. (Table 14-6)
 - When the defect involves keratins 5 and 14 a split through lowest part of basal keratinocyte and the formation of bullae occurs.
 - All types of EB patients exhibit fragile skin, blisters, scarring, nail dystrophy, milia and scarring alopecia.

- Dominant subtypes
 - Localized EBS:
 - *Weber-Cockayne type*: localized lesions on the palms and soles, hyperhidrosis, most common type of EBS
 - Generalized EBS:
 - *Koebner type*: AD, presents during infancy and early childhood, generalized lesions (extremities are more severely involved), palmoplantar hyperkeratosis
 - *Dowling-Meara type* (EBS herpetiformis): AD, onset at birth, herpetiform grouped vesicles on annular erythematous base, nail dystrophy, oral mucosal involvement
- Other subtypes:
 - *EB simplex with mottled pigmentation*: onset at birth, generalized distribution, mottled or reticulate brown pigmentation
 - *Superficial type*: disruption of the stratum granulosum
 - *Acantholytic type*: hyperkeratosis and bullae of the palms and soles
- Recessive subtypes:
 - *Muscular dystrophy type*: abnormality of plectin 1 (plectin 1/ intermediate filament binding protein), hemidesmosomal protein 1 (HD1/ protein needed for hemidesmosome formation), causes split through lowest part of basal keratinocyte, muscular dystrophy occurs in the limb-girdle
 - *Type unrelated to muscular dystrophy*: homozygous K14 nonsense mutation
 - *Skin fragility syndrome*: abnormal PKP1 (encodes the desmosome protein plakophilin 1), classified as a variant of acantholytic EB, but also considered a form of ectodermal dysplasia; formation of intraepidermal acantholysis;

TABLE 14-1 Ultrastructural Findings Among Major Types and Selected Subtypes of EB

EB Type or Subtype	Ultrastructural Site of Skin Findings	Other Ultrastructural Findings
EB simplex (EBS)		
EBS, localized	Basal layer	Split may spread to suprabasilar layer
EBS, DM	Basal layer in subnuclear cytoplasm	Dense, circumscribed clumps of keratin filaments (most commonly observed)
EBS-MD	Predominantly in basal layer, above level of HD attachment plaque	Reduced integration of keratin filaments with HD
EBS-AR	Basal keratinocytes	Absent or reduced keratin filaments within basal keratinocytes
EBSS	Split usually at interface between granular and cornified cell layers	—
EBS, lethal acantholytic	Suprabasal cleavage and acantholysis	Perinuclear retraction of keratin filaments
EBS, plakophilin-1 deficiency	Mid-epidermal cell-cell separation	Diminutive suprabasal desmosomes; perinuclear retraction of keratin filaments
EBS-PA	Lower basal layer, above level of HD plaque	Reduced integration of keratin filaments with HD
Junctional EB (JEB)		
JEB-H	Lamina lucida	Markedly reduced or absent HD; absent SBDP
JEB-nH	Lamina lucida	HDs may be normal or reduced in size and number
JEB-PA	Lamina lucida	Small HD plaques often with attenuated SBDP
Dominant dystrophic EB (DDEB)		
DDEB, generalized	Sub-lamina densa	Normal or decreased numbers of AFs
DDEB-BDN	Sub-lamina densa	Electron-dense stellate bodies within basal layer; reduced AFs
Recessive dystrophic EB (RDEB)		
RDEB, severe generalized	Sub-lamina densa	Absent or rudimentary AFs
RDEB, generalized other	Sub-lamina densa	Reduced or rudimentary-appearing AFs
RDEB-BDN	Sub-lamina densa	Electron-dense stellate bodies within basal layer; reduced AFs

AF, Anchoring fibril; AR, autosomal recessive; BDN, bullous dermolysis of the newborn; DM, Dowling-Meara; EBSS, EBS superficialis; H, Herlitz; HD, hemidesmosome; MD, muscular dystrophy; nH, non-Herlitz; PA, pyloric atresia; SBDP, sub-basal dense plate.

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TABLE 14-2 The Four Major EB Types

Level of Skin Cleavage	Major EB Type	Known Targeted Protein(s)
Intraepidermal ("epidermolytic")	EBS	Keratins 5 and 14; plectin; $\alpha 6\beta 4$ integrin; plakophilin-1; desmoplakin
Intra-lamina lucida ("lamina lucidolytic")	JEB	Laminin-332 (laminin 5); type XVII collagen; $\alpha 6\beta 4$ integrin
Sub-lamina densa ("dermolytic")	DEB	Type VII collagen
Mixed	Kindler syndrome	Kindlin-1

DEB, Dystrophic EB; EBS, EB simplex; JEB, junctional EB.

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TABLE 14-3 The Major EB Subtypes

Major EB Type	Major EB Subtypes	Targeted Protein(s)
EBS	Suprabasal EBS	Plakophilin-1; desmoplakin; ? others
	Basal EBS	Keratins 5 and 14; plectin; $\alpha 6\beta 4$ integrin
JEB	JEB-H	Laminin-332 (laminin-5)
	JEB, other	Laminin-332; type XVII collagen; $\alpha 6\beta 4$ integrin
DEB	Dominant DEB	Type VII collagen
	Recessive DEB	Type VII collagen
Kindler syndrome	—	Kindlin-1

DEB, Dystrophic EB; EBS, EB simplex; JEB, junctional EB.

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alopecia, palmoplantar keratoderma, painful fissures, nail dystrophy, cheilitis, hypohidrosis

- *EBS with pyloric atresia*: (possibly AR), widespread congenital absence of skin, pyloric atresia, malformed pinnae and nasal alae; joint contractures; cryptorchidism

Junctional Epidermolysis Bullosa (JEB)

- Autosomal recessive
 - Split within lamina lucida
 - Targeted proteins include: Laminin 5, type XVII collagen, $\alpha 6\beta 4$ Integrin (Table 14-7)
- Two main subtypes:
 - *JEB-Herlitz*: defect of laminin-5 gene (codes for an anchoring filament glycoprotein), more severe than other subtype with associated premature death, generalized blistering, multisystem disease: eyes (corneal, conjunctival), mucosa (tracheobronchial, oral, pharyngeal, esophageal, rectal, and genitourinary); delayed puberty, exuberant granulation, pitted teeth
 - *JEB-non-Herlitz*: defect found in laminin-5 and bullous pemphigoid antigen-2 (type XVII collagen, 180 kDa), milder form of JEB; corneal erosions, teeth with pitted enamel
- *Generalized atrophic benign EB (GABEB)*: ambient temperature causes increased blistering, blisters heal with atrophy
- *Junctional epidermolysis bullosa with pyloric atresia*: AR, defect in $\alpha 6\beta 4$ integrin gene; affects hemidesmosome, split within lamina lucida, pyloric atresia present at birth, rudimentary ears, GU malformations, may be associated with large areas of aplasia cutis, focal segmental glomerulosclerosis

TABLE 14-4 Antigenic Alterations in EB Skin

Antigen	Abnormal Staining in:	Usual Pattern of Staining
Keratin 14	EBS-AR	Absent or markedly reduced
Laminin-332 (laminin-5)	JEB-H	Absent or markedly reduced
	JEB-nH generalized	Reduced
Collagen	JEB-nH, generalized	Absent
	JEB-nH, localized	Reduced
Type VII collagen	RDEB, severe generalized	Absent or markedly reduced
	JEB-nH, localized	Reduced
Type VII collagen	RDEB, severe generalized	Absent or markedly reduced
	RDEB, generalized other	Reduced
	RDEB, inversa	Variable
	DEB-BDN (only during period of active blistering)	Granular staining within basal and suprabasal keratinocytes; absent or markedly reduced staining along DEJ
Plectin	EBS-MD	Absent or reduced
	EBS-PA	Absent or reduced
	EBS-Ogna	Reduced
$\alpha 6\beta 4$ Integrin	JEB-PA	Absent or reduced
	EBS-PA	Absent or reduced
	JEB-nH	Reduced
Kindlin-1	Kindler syndrome	Absent, reduced, or normal

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- *JEB inversa*
 - Blisters located in intertriginous areas, presents at birth, atrophic scarring, dystrophic or absent nails, intraoral erosions; esophagus and anus may be severely involved.
- *Laryngo-onycho-cutaneous syndrome* (LOC syndrome, Shabbir's syndrome): AR; associated with mutations in the $\alpha 3$ chain of laminin-332.; blisters commonly found on face and neck, onset first few months of life, hoarseness, exuberant granulation of conjunctiva and/or larynx.
- *JEB, late onset (EB progressive)*
 - AR, onset young adulthood or later, hyperhidrosis, absent dermatoglyphs; affects

hands, feet, elbows, and knees; nails are absent or dystrophic, intraoral erosions.

Epidermolysis Bullosa Dystrophica (Fig. 14-1)

- Autosomal dominant and recessive types
- Due to defects of type VII collagen found in the anchoring fibril protein and in most cases are related to COL7A1 gene mutations (Table 14-8)

Dominant Dystrophic Epidermolysis Bullosa

- Fewer anchoring fibrils (Type VII collagen)
- Subepithelial split below lamina densa
- *Generalized type (Pasini; Cockayne-Touraine)*: AD, Cockayne-Touraine: onset at birth with generalized

TABLE 14-5 Mutational Analyses and Inherited EB: Summary of Findings by EB Type and Subtype

EB Type	EB Subtype	Target Gene (Protein)	Types of Mutations Known
EBS	Suprabasal	PKP1 (plakophilin-1)	Spl, Del, NS
		<i>DSP</i> (desmoplakin)	NS, Del
	Basal	<i>KRT5</i> (keratin-5)	MS, NS, Del, Spl
		<i>KRT14</i> (keratin-14)	MS, NS, Del, Ins, Spl, in-frame del/ins
		<i>PLEC1</i> (plectin)	MS, NS, Del, Ins, in-frame del/ins
		<i>ITGA6, ITGB4</i> (alpha6β4 integrin)	MS, NS, Del, Ins, Spl
JEB	Herlitz	<i>LAMA3, LAMB3, LAMC2</i> (laminin-332)	NS, Del, Ins, Spl
	Other	<i>LAMA3, LAMB3, LAMC2</i> (laminin-332)	MS, NS, Del, Ins, Spl
		<i>COL17A1</i> (type XVII collagen)	MS, NS, Del, Ins, Spl
DEB	Dominant	<i>COL7A1</i> (type VII collagen)	MS Spl
	Recessive	<i>COL7A1</i> (type VII collagen)	MS Ins Del NS Spl
Kindler syndrome		<i>KIND1</i> (kindlin-1)	NS Spl Ins Del

Del, Deletion; *in-frame del/ins*, in-frame deletion and insertion; *Ins*, insertion; *MS*, missense mutation; *NS*, nonsense mutation; *Spl*, splice site mutation. In many cases with recessive inheritance, two different mutations are present in one individual compound heterozygosity.

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TABLE 14-6 EBS Subtypes

Major EBS Types	EBS Subtypes*	Targeted Proteins
Suprabasal	<i>Lethal acantholytic EB</i>	Desmoplakin
	<i>Plakophilin deficiency</i>	Plakophilin-1
	<i>EBS superficialis (EBSS)</i>	?
Basal	EBS, localized (EBS-loc) [†]	K5, K14
	EBS, Dowling-Meara (EBS-DM)	K5, K14
	EBS, other generalized (EBS, gen-nonDM; EBS, gen-nDM) [‡]	K5, K14
	<i>EBS-with mottled pigmentation (EBS-MP)</i>	K5
	EBS with muscular dystrophy (EBS-MD)	Plectin
	<i>EBS with pyloric atresia (EBS-PA)</i>	Plectin; EBS, 6β4 integrin
	<i>EBS, autosomal recessive (EBS-AR)</i>	K14

EBS, EB simplex.

*Rare variants shown in italics.

[†]Previously called EBS, Weber-Cockayne.

[‡]Includes patients previously classified as having EBS-Koebner.

TABLE 14-7 Junctional EB Subtypes

Major JEB Subtype	Subtypes*	Targeted Proteins
JEB, Herlitz (JEB-H)	—	<i>Laminin 5</i> (Laminin-332)
JEB, other (JEB-O)	JEB, non-Herlitz, generalized (JEB-nH gen) [†]	<i>Laminin 5</i> (Laminin-332); type XVII collagen
	JEB, non-Herlitz, localized (JEB-nH loc)	Type XVII collagen
	JEB with pyloric atresia (JEB-PA)	$\alpha 6\beta 4$ Integrin
	<i>JEB, inversa (JEB-I)</i>	<i>Laminin 5</i> (Laminin-332)
	<i>JEB, late onset (JEB-lo)[‡]</i>	?

*Rare variants shown in italic type.

[†]Formerly known as generalized atrophic benign EB (GABEB).

[‡]Formerly known as EB progressive.

blistering, hypertrophic lesions, acral distribution, dystrophic nails

- *Pasini variant*: onset in infancy with more extensive blistering that heals with atrophic scars and milia; Albopapuloid lesions (white papular lesions) on the trunk, intra oral lesions
- Transient bullous dermolysis of the newborn is subtype that resolves by age 1 or 2 years



FIGURE 14-1 Dystrophic epidermolysis bullosa. (Courtesy of Dr. Joy Kunishige.)

TABLE 14-8 Dystrophic EB Subtypes

	Targeted Protein	All Subtypes*
DDEB	DDEB, generalized (DDEB-gen)	Type VII collagen
	<i>DDEB, acral (DDEB-ac)</i>	
	<i>DDEB, pretibial (DDEB-Pt)</i>	
	<i>DDEB, pruriginosa (DDEB-Pr)</i>	
	<i>DDEB, nails only (DDEB-na)</i>	
	<i>DDEB, bullous dermolysis of the newborn (DDEB-BDN)</i>	
DDEB	DDEB, generalized (DDEB-gen)	Type VII collagen
	<i>DDEB, acral (DDEB-ac)</i>	
	<i>DDEB, pretibial (DDEB-Pt)</i>	
	<i>DDEB, pruriginosa (DDEB-Pr)</i>	
	<i>DDEB, nails only (DDEB-na)</i>	
	<i>DDEB, bullous dermolysis of the newborn (DDEB-BDN)</i>	
DDEB	DDEB, generalized (DDEB-gen)	Type VII collagen

DDEB, Dominant dystrophic EB; RDEB, recessive dystrophic EB.

* Rare variants in italic type.

Recessive Dystrophic Epidermolysis Bullosa (RDEB)

- Absent anchoring fibrils (Type VII collagen)
- Subepithelial split below lamina densa
- *RDEB mitis*: involves acral areas and nails, localized form
- *Severe generalized (Hallopeau-Siemens type)*: generalized lesions and clubbing of the digits, pseudosyndactyly of fingers and toes (mitten hand deformity), flexion contractures, esophageal strictures and webs, stenosis of urethra and anal canal, phimosis, corneal scarring, squamous cell carcinoma can develop in non-healing wounds; glomerulonephritis, renal amyloidosis; IgA nephropathy; chronic renal failure (CRF); cardiomyopathy; delayed puberty; osteoporosis most severe type
- *Generalized other (non-Hallopeau-Siemens type)*: blisters present at birth, GI abnormalities
- *RDEB inversa*: onset at birth, distribution of blistering is intertriginous, acral, lumbosacral, axial; esophageal strictures, anal strictures and fissures, oral erosions, partial fusion of the digits with contractures, females with vaginal involvement and scarring.
- *RDEB centripetalis*: initial acral distribution of blisters with centripetal spread, milia, atrophic scarring, nail dystrophy

Other Dystrophic EB Subtypes

- *Acral*:
 - Dominant dystrophic EB (DDEB) or recessive dystrophic EB (RDEB):
 - Blisters located on hands and feet, dystrophic or absent nails; develops during infancy
- *Pretibial*:
 - DDEB and RDEB: blisters develop during birth or infancy, located on pretibial area, hands and feet; nails (fingers and toes), lichen planus like lesions, dystrophic or absent nails
- *DEB pruriginosa*:
 - Rare variant of DEB due to COL7A1 dominant and recessive mutations, which is characterized by severe itching and lichenoid or nodular prurigo-like lesions, mainly involving the extremities
- *DDEB nails only*: onset at birth or infancy
- *Kindler syndrome*:
 - Autosomal recessive
 - Combination of features of *dystrophic epidermolysis bullosa* and *congenital poikiloderma* (e.g., Rohmand Thompson)
 - Due to a mutation in the gene *KIND 1* encoding for kindlin-1: component of focal contacts in basal keratinocytes: multiple cleavage planes (intraepidermal, junctional, or sublamina densa)
 - Generalized blistering, onset at birth, poikiloderma; photosensitivity; mental retardation (rare);

bone abnormalities (rare), gingival hyperplasia, cutaneous atrophy, colitis (may be severe); esophagitis, urethral strictures

Diagnosis of Epidermolysis Bullosa

- Electron microscopy on biopsy at the edge of a fresh blister, include both unblistered and blistered skin
- Immunofluorescent studies to detect abnormal protein antigens and serial monitoring of the patient
- Skin biopsy
- Upper GI series or endoscopy
- DNA mutation analysis
- Treatment: symptomatic care

DISORDERS OF PIGMENTATION

Neurofibromatosis I (Von Recklinghausen Disease)

- Autosomal dominant disease
- Defect of NF1 gene (chromosome 17q11.2) codes for neurofibromin: tumor suppressor; down-regulates activity of RAS (associated with increased cell proliferation and possible tumor formation)
- Neurofibromin, also positively regulates intracellular cyclic adenosine monophosphate (cAMP) levels, which modulate cell growth and differentiation in the brain.
- Diagnosis: requires two or more of the following features:
 - > 6 Café-au-lait macules
 - 1.5 cm or larger in postpubertal individuals
 - 0.5 cm or larger in prepubertal individuals
 - Two or more neurofibromas or one plexiform neurofibroma (Fig. 14-2)
 - Most common tumor seen in patients with NF1
 - Axillary (Crowe's sign) or inguinal freckling
 - Optic glioma: tumor of the optic pathway
 - Two or more lisch nodules: pigmented spots that are hamartomas of iris
 - Distinctive bony lesion: dysplasia of the sphenoid wing, dysplasia or thinning of long bone cortex
 - First-degree relative with NF-1
- Clinical features
 - *Café-au-lait spots (CALs)*: often present at birth; flat, evenly pigmented macules or patches, may fade as patient ages, in which case, Wood's lamp may aid in diagnosis
 - *Skinfold freckling*: usually not apparent at birth but appears later in childhood
 - *Lisch nodules* are asymptomatic, raised, pigmented hamartomas of the iris; diagnosis by slit lamp. They are present in most adult NF1 patients.
 - *Discrete neurofibromas*: benign peripheral nerve sheath tumors, develop during adolescence. They are composed of a mixture of cell types including

Schwann cells, fibroblasts, mast cells, and vascular elements.

- *Plexiform neurofibromas*: may diffusely involve nerve, muscle, connective tissue, vascular elements, and overlying skin. Since they can remain clinically silent for many years, diagnosis may be incidental by imaging studies or by the effects of the tumor on associated organs or structures.



FIGURE 14-2 Neurofibromas. (Reprinted with permission from Wolff K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- *Optic pathway gliomas*: typically arise in young children, second most common tumor in NF1 patients, low-grade pilocytic astrocytoma that typically arises in the optic nerve and chiasm, hypothalamus, brainstem, and/or cerebellum
- *Increased risk of malignancy*: neurofibrosarcoma, astrocytoma, rhabdomyosarcoma, myelogenous leukemia, malignant peripheral nerve sheath tumor
- *Other neurological complications*: macrocephaly, hydrocephalus, cognitive impairment, headaches, seizures, and cerebral ischemia
- *Learning disabilities*: common in children with NF1, but frank mental retardation (IQ < 70) is uncommon
- *Skeletal abnormalities*: Kyphoscoliosis
- *Endocrine disease*: (acromegaly, cretinism, hypothyroidism, hyperparathyroidism, precocious puberty)
- Variants of NF-1:
 - *Segmental or mosaic NF1*: when one of the two NF1 genes sustains a mutation during fetal development; a localized area of the developing fetus is affected.
 - *Watson's syndrome*: multiple café au lait spots, dull intelligence, short stature, pulmonary valvular stenosis, and only a small number of neurofibromas, and lisch nodules

TABLE 14-9 Age-Dependent Manifestations and Management of NF1

Age	Manifestations and Management
1–2 years	<ul style="list-style-type: none"> • Café-au-lait macules • Plexiform neurofibromas • Tibial Dysplasias (anterolateral bowing of lower leg): may require orthopedic referral
3–5 years	<ul style="list-style-type: none"> • Skinfold Freckling • Lisch nodules • Optic Pathway Gliomas: requires serial neurologic, ophthalmologic, and MRI scans once detected. Further management is warranted if there is tumor progression. • Learning disabilities: requires planning with parents and teachers and early intervention if detected. • Precocious puberty: requires endocrinologic and radiographic evaluation • Plexiform Neurofibromas: requires regular follow-up
Late childhood and early adolescence	<ul style="list-style-type: none"> • Dermal Neurofibromas • Plexiform Neurofibromas: requires regular follow-up • Scoliosis: requires orthopedic evaluation for possible bracing and/or surgery
Lifelong	<ul style="list-style-type: none"> • Neurofibromas • Pain • Plexiform Neurofibromas: requires regular follow-up • Malignant Peripheral Nerve Sheath Tumor (MPNST) • Other Malignant Neoplasms

- *Neurofibromatosis-Noonan syndrome (NFNS)*: children with NF1 also display the following features (similar to Noonan's syndrome): pectus excavatum, hypertelorism, short stature
- Management (Table 14-9)
 - Requires a multidisciplinary approach.
 - Abnormalities on the visual examination should prompt MRI evaluation ("screening" or "baseline" MRI evaluations, as they are not predictive)
 - Serial ophthalmologic and neurologic exams.

Neurofibromatosis II (Bilateral Acoustic Neurofibromatosis)

- Autosomal dominant disease
- Defect of NF2 gene coding for schwannomin or merlin (chromosome 22q11)
- Diagnosis: requires either of the following:
 - Bilateral cranial nerve eight masses (acoustic neuromas)
 - First-degree relative with NF-2 plus either unilateral eighth nerve mass or two of the following: neurofibroma, schwannoma, optic glioma, meningioma, juvenile posterior subcapsular opacity
- Clinical
 - *Unilateral hearing loss* with or without tinnitus, dizziness or imbalance
 - *Mononeuropathy*, mainly affects the facial nerve, resulting in a Bell's-like palsy
 - *Spontaneous malignant transformation of schwannomas* to malignant peripheral nerve sheath tumours (MPNST); more than 10 times as likely to occur following radiation treatment
 - *CNS tumors*: meningiomas, the second most common tumor in NF2 patients, occur supratentorially in the falx and around the frontal, temporal, and parietal regions. Ependymomas and gliomas usually located in the cervical spine or brain stem.
 - *Ophthalmic involvement*: cataracts, optic nerve meningiomas and retinal hamartomas may cause visual loss
 - *Cutaneous tumors*: schwannomas with occasional neurofibromas
- Diagnosis
 - Magnetic resonance imaging (MRI) scan with gadolinium enhancement
 - Pathology: schwannomas, encapsulated tumors of pure Schwann cells, grow around the nerve; may contain blood vessels and have areas of sheets in intertwining fascicles (Antoni A) and looser arrangements (Antoni B). S-100 protein and vimentin positive.
- Treatment
 - Management by a multidisciplinary team

- Microsurgery and radiation treatment for patients with aggressive tumors
- Visual and audiological testing

VASCULAR-RELATED DISORDERS

Von Hippel-Lindau Syndrome

- Autosomal dominant
- *VHL* gene (chromosome 3); tumor suppressor gene
- VHL gene affects the VCB-CUL2 complex, which targets a protein called hypoxia-inducible factor (HIF). HIF is involved in cell division and the formation of new blood vessels.
- Presents by fourth decade
- Diagnostic criteria: (1) more than one hemangioblastoma in the CNS, (2) one CNS hemangioblastoma and visceral manifestations of VHL, or (3) one manifestation and a known family history of VHL.
- Clinical findings
 - *Common tumors*: cerebellar, medullary, or spinal cord hemangioblastomas with increased intracranial pressure, spinal cord compression; retinal hemangioblastomas with visual impairment, and renal cell carcinoma (RCC)
 - *Endocrine tumors*: pheochromocytoma (usually intra-adrenal), adrenal carcinoma, pancreatic islet cell cancers
 - *Cysts*: renal and pancreatic
 - Phenotypic variability (types of presentation of VHL patients):
 - *Type 1*: retinal or CNS hemangioblastomas and RCC but not pheochromocytoma
 - *Type 2*: at least one affected individual has pheochromocytoma in the family; Type 2A: retinal and CNS hemangioblastomas are present, but rarely RCC occur; Type 2B hemangioblastomas, RCC and pheochromocytoma
 - *Other clinical features*: polycythemia secondary to increased erythropoietin, capillary malformation on head and neck, endolymphatic sac neoplasm, cardiac rhabdomyoma, hepatic cyst, adenoma, and/or angioma, carcinoid of the common bile duct, bone cysts or hemangiomas, café-au-lait spots
- Screening and management (Table 14-10)
 - Imaging modalities: ultrasonography, CT, MRI, radionuclide studies, and angiography

Ataxia-Telangiectasia (Louis-Bar Syndrome)

- Autosomal recessive
- Mutation in *ATM* gene (ataxia-telangiectasia mutated/located on chromosome 11q22-23); codes for protein kinase, involved in cellular responses

TABLE 14-10 Screening of Patients With VHL and At-Risk Relatives (Cambridge Protocol)

Type of Patient	Recommended Screening
Affected asymptomatic patient	<ul style="list-style-type: none"> • Annual physical examination and urine test • Annual direct and indirect ophthalmoscopy • Annual fluorescein angiography or angiography • Annual renal ultrasonographic examination • MRI or CT scan of the brain every 3 years to age 50 years then every 5 years thereafter • Abdominal CT scanning every 3 years (more often if multiple renal cysts are present) • Annual 24-hour urine collection for vanillylmandelic acid (VMA) levels
At-risk relatives – same protocol as above with additional age based exams	<ul style="list-style-type: none"> • Annual direct and indirect ophthalmoscopy from age 5 years • Annual fluorescein angiography or angiography from age 10 years until age 60 years • MRI or CT scanning of the brain every 3 years from ages 15–40 years, then every 5 years until age 60 years • Abdominal CT scanning every 3 years from ages 20–65 years

to DNA damage and cell cycle control; defective DNA repair with increased sensitivity to ionizing radiation

- Clinical findings
 - Progressive ataxia, presenting symptom when a child begins to walk; affects the extremities first and then speech; due to depletion of granular and Purkinje cells in cerebellum
 - Oculocutaneous telangiectasias by ages 3 to 6 years
 - Respiratory infections owing to decreased humoral and cellular immunity; decrease in the total number of CD4+ cells
 - Decreased development of thymus gland
 - Malignancies: 40% non-Hodgkin's lymphomas, 25% leukemias, 25% (most leukaemias and lymphomas are of T-cell origin); assorted solid tumors (adenocarcinoma of the stomach, dysgerminoma, gonadoblastoma and medulloblastoma) and 10% Hodgkin's lymphomas.
 - Hypogonadism
- Diagnosis (Table 14-11)
- Treatment, symptom based
 - *Basal ganglia dysfunction*: L-DOPA derivatives, dopamine agonists and, occasionally, anticholinergics
 - *Loss of balance, speech and coordination*: amantadine, fluoxetine or buspiron
 - *Tremors*: gabapentin, clonazepam or propranolol
 - *Hypogammaglobulinaemia with antibody deficiency*: immune globulin replacement
 - *Sinopulmonary infections*: antibiotics
 - *Lymphoid hematopoietic malignancies*: chemotherapy

TABLE 14-11 Laboratory Evaluation of A-T Patients

Alpha-fetoprotein	Elevated
Radiation response	Hypersensitive
p53 stabilization	Defective
ATM mutations	Yes
ATM protein	Absent/Detectable
ATM kinase activity	Absent
ATM signalling pathways	Defective

Hereditary Hemorrhagic Telangiectasia (HHT/Osler-Weber-Rendu Syndrome)

- Autosomal dominant
- Mutation of:
 - HHT1 gene containing endoglin (chromosome 9q33–34); it encodes a membrane glycoprotein found on human vascular endothelial cells
 - HH2 gene contains the *activin-like receptor kinase (ALK-1)* on chromosome 12q; it encodes transforming growth factor- β receptors
- Presents in childhood to early adulthood
- Diagnosis
 - Based on the Scientific Advisory Board of the HHT Foundation International Inc. consensus on clinical diagnostic criteria—Curaçao Criteria for HHT:
 - *Definite*: three criteria are present
 - *Possible or suspected*: two criteria are present
 - *Unlikely*: fewer than two criteria are present

- Criteria
 - Epistaxis: spontaneous, recurrent nose bleeds
 - Telangiectasias: characteristic sites – lips, oral cavity, fingers, nose
 - Visceral lesions: gastrointestinal telangiectasia (with or without bleeding), pulmonary AVM, hepatic AVM, cerebral AVMs, spinal AVM
 - Family history: first-degree relative with HHT according to these criteria
- Clinical findings
 - Triad of epistaxis, telangiectasia, and family history
 - Telangiectasias in third to fourth decade: face, palms, soles, conjunctiva, oral mucosa
 - Recurrent epistaxis
 - Gastrointestinal telangiectasias with hemorrhage
 - Hepatic or pulmonary AVMs: causing right-to-left shunts (most serious problem)
 - Neurologic involvement: seizures, and focal neurologic symptoms
- Laboratory and imaging studies
 - Complete blood count: evaluate for anemia or polycythemia
 - Arterial blood gas
 - MRI to check for CNS and pulmonary AVMs
- Treatment
 - Symptomatic medical and surgical care to decrease the amount of bleeding experienced by the patient
- Diagnostic criteria (Table 14-12)
- Clinical findings
 - Asymmetric overgrowth of tissues and neoplasms
 - *Cutaneous involvement*: cerebriform connective tissue nevi, epidermal nevi, vascular malformations, lipomas, lipohypoplasia, and dermal hypoplasia
 - *Extracutaneous manifestations*: skeletal overgrowth (macrocephaly, frontal bossing), visceral overgrowth (pharyngeal or vocal cord), tumors (epibulbar dermoid of the eye, ovarian cystadenoma), pulmonary and intracranial cysts, hernias, hydrocele, and undescended or absent testes, venous and lymphatic malformations
 - May be associated with neurofibromatosis 1
- Treatment: multidisciplinary approach

Klippel-Trenaunay Syndrome

- Sporadic inheritance
 - Triad of (1) capillary vascular malformation (port wine stain), (2) varicose veins and/or venous malformation, and (3) soft tissue and/or bony hypertrophy
- Clinical findings
 - Usually affects one limb; most commonly leg, then arm, and trunk
 - Capillary, venous, and lymphatic malformations
 - Soft tissue and bony hypertrophy (Fig. 14-3)
 - Other features: phleboliths, deep venous thromboses, pulmonary emboli, thrombophlebitis, cellulitis, intraosseous vascular malformations,

Proteus Syndrome

- Sporadic inheritance
- PTEN gene mutation

TABLE 14-12 Diagnostic Criteria for Proteus Syndrome

Mandatory General Criteria	Mosaic Distribution of Lesions, Progressive Course, Sporadic Occurrence
Specific criteria (A, or 2 from group B, or 3 from group C)	
Group A	Connective tissue nevus
Group B	Epidermal nevus Disproportionate overgrowth (1 or more) Limbs, skull, external auditory meatus, vertebra, viscera (spleen and/or thymus) Specific tumors before the end of the 2nd decade (either one): bilateral ovarian cystadenomas, parotid monomorphphic adenoma
Group C	Dysregulated adipose tissue (either one): lipomas, regional absence of fat Vascular malformations (1 or more): capillary, venous, and/or lymphatic Facial phenotype: dolichocephaly, long face, low nasal bridge, wide or anteverted nares, open mouth at rest

Reprinted with permission from Nguyen D, Turner JT, Olsen C, Biesecker LG, Darling TN: Cutaneous manifestations of proteus syndrome: correlations with general clinical severity. *Arch Dermatol* 2004 Aug;140(8):947–953.



FIGURE 14-3 Klippel-Trenaunay syndrome in a patient with hypertrophy of left side of face and tongue. (Reprinted with permission from Fuster V, O'Rourke RA, Walsh R, Poole-Wilson P: *Hurst's The Heart*, 12th Ed. New York: McGraw-Hill; 2008.)



FIGURE 14-4 Right facial capillary malformation. (Reprinted with permission from Wolff K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

arthritis, neuropathic pain, spina bifida, hypospadias, polydactyly, syndactyly, oligodactyly, hyperhidrosis, decalcification of involved bones

- Parkes-Weber variant has AV fistulas
- Cutaneous manifestations: chronic venous insufficiency with stasis dermatitis, lipodermatosclerosis, varicosity, atrophy blanche, corona phlebectatica, and, ultimately, breakdown of the skin with ulcerations, hypertrichosis
- Treatment: compression stockings, surgical intervention, sclerotherapy, or endovascular laser ablation depending on patient's symptoms
- Cellulitis and thrombophlebitis: analgesics, elevation, antibiotics, and corticosteroids
- Limb discrepancies: shoe inserts or orthopedic surgery

Sturge-Weber Syndrome (Encephalotrigeminal Angiomatosis)

- Sporadic inheritance
- Neural crest defect

• Clinical findings

- *Facial port-wine stain* (Fig. 14-4)
 - Presents at birth and is typically unilateral (85%), involving the ophthalmic (V_1), maxillary (V_2), and/or mandibular (V_3) divisions of the trigeminal nerve.
 - Occurs with ipsilateral leptomeningeal vascular anomalies (capillary, venous, and AV malformations) and/or choroidal vascular lesions with glaucoma (unilateral)
 - Involvement of the entire V_1 distribution may indicate underlying neurological and/or ocular disorders
- *Roach classification scale*:
 - Type I – Both facial and leptomeningeal angiomas (LA); may have glaucoma
 - Type II – Facial angioma alone (no CNS involvement); may have glaucoma
 - Type III – Isolated LA; usually no glaucoma
- Neurologic complications: seizures, psychomotor delay in infancy, headaches and migraines, hemiparesis
- Tram-track calcification in cortex

- Diagnostic tests
 - Head CT and MRI: diagnosis of intracranial calcifications and leptomeningeal angiomas
 - CSF analysis: elevated protein
- Treatment
 - Port-wine stains: laser (pulsed dye laser)
 - Seizures: anticonvulsants for focal
 - Headaches: NSAIDs
 - Medical or surgical control of intraocular pressure

CONNECTIVE TISSUE DISORDERS

Ehler's-Danlos Syndrome

- Connective tissue disorder characterized by skin extensibility, tissue fragility, and joint hypermobility
- Collagen V defect, less frequently tenascin-X
- Autosomal dominant
- Clinical
 - Types of Ehlers Danlos:
 - *Classical (EDS I and II)*
 - ▲ AD, abnormal type V collagen (*COL5A1*, *COL5A2* mutations)
 - △ Clinical findings: skin hyperextensibility, easy bruising, wide, atrophic scars, joint hypermobility with sprains, dislocations, muscle hypotonia, hernias
 - △ May have cardiac defects: mitral valve defects
 - △ Molluscoid pseudotumors: spongy tumors found over scars and pressure points (more common in type 1EDS)
 - △ Spheroids (fat-containing cysts)
 - *Hypermobility (EDS III)*
 - ▲ Autosomal dominant
 - ▲ Clinical findings: joint hypermobility with recurrent dislocations, chronic pain, mild skin hyperextensibility
 - △ Mitral valve prolapse
 - *Vascular (type IV, ecchymotic or arterial type)*
 - ▲ Autosomal dominant, collagen III defect (*COL3A1*)
 - ▲ Clinical findings: thin, translucent skin with bruising, characteristic facies (prominent eyes, small lips, pinched nose, hollow cheeks and lobeless ears), hypermobility of small joints with dislocation, varicose veins; arterial, intestinal, and uterine rupture which may cause sudden death; keloids, molluscoid pseudotumors, pneumothorax, inguinal hernia
 - ▲ Cerebrovascular bleeding in younger patients; intracranial aneurismal rupture, spontaneous carotid-cavernous sinus fistula and cervical artery aneurysm
- *Kyphoscoliosis (type VI or ocular-scoliotic type)*
 - ▲ Autosomal recessive
 - ▲ Lysyl hydroxylase deficiency (*LH1* gene)
 - ▲ Clinical findings: generalized joint laxity with severe hypotonia, progressive scoliosis; unable to ambulate by early adulthood, scleral fragility, prone to global rupture, retinal hemorrhage and detachment, glaucoma, discolored sclera, arterial rupture, marfanoid habitus, osteopenia, osteoporosis
 - ▲ LH can be measured in the amniotic fluid
- *Arthrochalasia (formerly VIIA and B)*
 - ▲ Autosomal dominant
 - ▲ Deficiency of proA1 or proA2 chains of collagen type I
 - ▲ Clinical findings: congenital bilateral hip dislocations, joint hypermobility with subluxations, kyphoscoliosis, mild osteopenia, skin laxity with bruising, atrophic scars, muscle hypotonia, short stature
- *Dermatosparaxis (type VIIC)*
 - ▲ Autosomal recessive
 - ▲ N-terminal peptidase of type I collagen I (*ADAMTS2* gene)
 - ▲ Clinical findings: severe skin fragility, redundant sagging skin (resembles cutis laxa), easy bruising, large hernias, premature rupture of membranes at delivery, no impairment of wound healing
- *Other types*
 - ▲ X-linked form (formerly type V)
 - △ X-linked recessive pattern
 - △ Clinical findings: skin laxity, orthopedic abnormalities
 - ▲ Periodontal (formerly type VIII)
 - △ AD
 - △ Clinical findings: gingival inflammation and resorption with loss of permanent teeth; variable presentation of skin laxity, joint hyperextensibility, and bruising
 - ▲ X-linked cutis laxa (formerly type IX)
 - △ X-linked recessive
 - △ Clinical findings: occipital bony prominences, poor healing with scarring, intracellular copper-dependent enzymes, chronic diarrhea with orthostatic hypotension
 - △ Fibronectin (formerly type X) and benign hypermobile joint syndrome (formerly type XI)

Osteogenesis Imperfecta (OI)

- Characterized by increased bone fragility and low bone mass.

TABLE 14-13 Characteristics of Osteogenesis Imperfecta (OI)

OI Subtype	Characteristics
I	Thin skin, blue sclera Lax joints, kyphosis, abnormal dentition Aortic valve disease, mitral valve prolapsed, long bone fractures, vertebral compression fractures
II	In utero fractures, limb avulsion at delivery Perinatal death common due to respiratory insufficiency following rib fractures Aortic valve disease, blue sclera
III	In utero fractures Progressive scoliosis, limb bowing, crippling deformity Blue sclera, triangular facies, short stature
IV	Fractures at birth, abnormal teeth Improvement with age

- Majority of patients (about 90%) have a mutation in COL1A1 or COL1A2, the genes encoding collagen type I (found in bone)
- Patients have low trabecular bone mineral density and thin cortices, and also small, slender bones.
- Mostly autosomal dominant
- Four main subtypes with different mutations resulting in varying severity of disease (Table 14-13)
- *Other subtypes*: non-collagen related defects
 - Type V: autosomal dominant (genetic defect unknown) moderate to severe bone fragility, irregular mesh-like appearance of lamellar bone
 - Type VI: autosomal recessive. Moderate to severe skeletal fragility; bone biopsy shows lamellae with fish like appearance and excessive osteoid.
 - Type VII: autosomal recessive. rhizomelia, coxa vera, reduction in expression of cartilage-associated protein (CRTAP)
- All characterized by osseous fragility
- May develop hearing loss due to otosclerosis

Marfan's Syndrome

- Autosomal dominant; mutation in fibrillin-1 (*FBN1*), chromosome 15; main component of extracellular microfibrils associated with elastin within elastic fibers

- Diagnosis: based on clinical criteria (Ghent nosology). Major and minor criteria of the following organ systems are evaluated in the patient: ocular, skeletal, integumental, respiratory, and cardiovascular. Major criteria in two systems with involvement of a third system are needed to make an unequivocal diagnosis.
- Criteria include:
 - Skeletal system (two of the components comprising the major criterion, or one component comprising the major criterion plus two of the minor criteria)
 - *Major criteria*: presence of at least four of the following manifestations: pectus carinatum, pectus excavatum requiring surgery, reduced upper to lower segment ratio or arm span to height ratio > 1.05 , positive wrist and thumb signs, scoliosis of $> 20^\circ$ or spondylolisthesis, reduced extension of the elbows ($< 170^\circ$), medial displacement of the medial malleolus causing pes planus, protrusio acetabulae of any degree (ascertained on x-ray)
 - *Minor criteria*: pectus excavatum of moderate severity, joint hypermobility, highly arched palate with dental crowding, facial appearance (dolicocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)
 - Ocular system (two of the minor criteria)
 - *Major criterion*: ectopia lentis
 - *Minor criteria*: abnormally flat cornea (as measured by keratometry), increased axial length of globe (as measured by ultrasound), hypoplastic iris or hypoplastic ciliary muscle causing a decreased miosis
 - Cardiovascular system (major criterion or only one of the minor criteria)
 - *Major criteria*: dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva, or dissection of the ascending aorta
 - *Minor criteria*: mitral valve prolapse with or without mitral valve regurgitation, dilatation of main pulmonary artery, in absence of valvular or peripheral pulmonic stenosis or any other obvious cause, under the age of 40 years, calcification of the mitral annulus below the age of 40 years, or dilatation or dissection of the descending thoracic or abdominal aorta below the age of 50 years
 - Pulmonary system (one of the minor criteria must be present)
 - *Major criteria*: none
 - *Minor criteria*: spontaneous pneumothorax, or apical blebs (ascertained by chest radiography)

- Skin and integument (major criterion or one of the minor criteria)
 - *Major criterion*: lumbosacral dural ectasia by computed tomography or magnetic resonance imaging
 - *Minor criteria*: striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy or repetitive stress, or recurrent or incisional herniae
- Family history (one of the major criteria must be present)
 - *Major criteria*: having a parent, child, or sibling who meets the diagnostic criteria listed below independently, presence of a mutation in FBN1 known to cause the Marfan syndrome, or presence of a haplotype around FBN1, inherited by descent, known to be associated with unequivocally diagnosed Marfan syndrome in the family
 - *Minor criteria*: none
- Requirements for the diagnosis of Marfan's syndrome
 - *For the index case*: major criteria in at least two different organ systems and involvement of a third organ system
 - *For a family member*: presence of a major criterion in the family history and one major criterion in an organ system and involvement of a second organ system
- Course: premature death secondary to cardiovascular defects
- Treatment: surgery, beta-blockers

Cutis Laxa (Generalized Elastolysis)

- Categorized by mode of inheritance and phenotypes: autosomal dominant, autosomal recessive (CL type I, CL type II, and type III-de Barsy syndrome), X-linked recessive (occipital horn syndrome), or acquired
- Characterized by redundant, loose and inelastic skin.
- Genetic defects: AD- ELN gene (elastin), autosomal recessive- fibulin-5 gene (FBLN5), or x-linked recessive-ATP7A
- Acquired cases: associated with penicillin, penicillamine, complement deficiency, lupus, amyloid, erythema multiforme, contact dermatitis, and Sweet's syndrome
- Clinical findings
 - *Autosomal recessive*:
 - *Cutis laxa, type I*: perinatal form, presents with pulmonary and other internal manifestations, leading to premature death
 - *Cutis laxa type II*: (also called *cutis laxa with joint laxity and developmental delay*); presents with sagging jowls, epicanthic folds, anti-mongoloid slant, maxillary hypoplasia, blue sclera, depressed nasal bridge, apparent ocular hypertelorism, and long philtrum, growth

retardation, developmental delay, microcephaly, wrinkling of skin on the abdomen, hernia, joint laxity, and dislocation

- *de Barsey syndrome*: rare type, associated with cutis laxa, retarded psychomotor development and corneal clouding due to degeneration of the tunica elastica of the cornea, growth retardation, may be pseudoathetoid movements
- *Autosomal dominant*: benign course; primarily, skin involvement, infrequent systemic complications, normal life expectancy
- *X-linked recessive*: skin laxity, skeletal and genitourinary tract abnormalities
- Histology: special elastin specific stains (Verhoeff-van Gieson and orcein) show loss, fragmentation, or both, or decreased number of elastic fibers

Pseudoxanthoma Elasticum (Grönblad-Strandberg Syndrome) (Fig. 14-5)

- Autosomal recessive more common than autosomal dominant
- *ABCC-6* gene, chromosome 16p; encodes multi-drug resistance associated protein 6 (MRP6), which belongs to the ABC (ATP binding cassette) transmembrane transporter family of proteins.
- D-Penicillamine implicated in drug-associated cases
- Progressive fragmentation and calcification of elastic fibers in skin, blood vessels, and Bruch's membrane of the eye
- Clinical findings
 - Redundant intertriginous skin

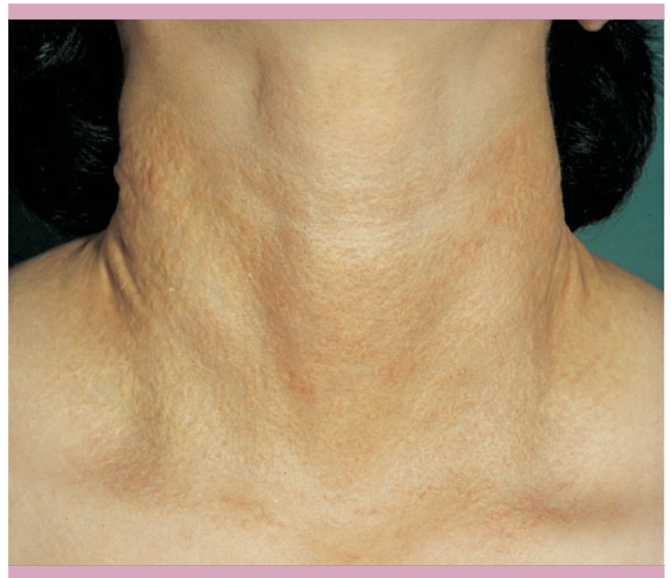


FIGURE 14-5 Pseudoxanthoma elasticum. (Reprinted with permission from Wolff K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- “Plucked chicken” or “gooseflesh” appearing skin with yellow papules typically developing on the neck and may coalesce into plaques; other areas affected include antecubital and popliteal fossae, axillae, inguinal, and periumbilical areas. Mucosal membranes may also be affected. Lesions are asymptomatic.
 - Affected skin may become lax and wrinkled.
 - *Perforating PXE*: occurs with extrusion of calcium deposits
 - *Ocular manifestations*: angioid streaks in Bruch’s membrane (seen in 85% of patients): irregular, reddish-brown, or grey lines that radiate from the optic disc. They are due to degenerated and calcified elastic fibers of the retina that causes breaks in Bruch’s membrane. The earliest eye finding is a peau d’orange appearance (yellowish mottled pigmentation) of the retina. Other findings: colloid bodies, macular degeneration, optic nerve head drusen (whitish-yellow irregularities of the optic disc), and “owl’s eyes” (paired hyperpigmented spots).
 - *Cardiovascular manifestations*
 - Claudication, hypertension, myocardial infarction (MI), cerebrovascular accident (CVA), coronary artery disease (CAD), renovascular hypertension, congestive cardiac failure, renal failure
 - *Gastrointestinal bleeds*: (seen in 10% of patients) due to calcified submucosal vessels
 - **Diagnostic criteria**
 - *Major*: characteristic skin lesions: cobblestone lesions in flexural areas, characteristic eye findings: angioid streaks, peau d’orange retinal appearance, maculopathy, characteristic histologic findings seen with elastic tissue and calcium stains.
 - *Minor*: characteristic histologic findings of non-lesional skin; family history of PXE in first degree relatives
 - *Histology*: hematoxylin-eosin stains—elastic fibers are basophilic because of the calcium deposition; fibers fragmented, swollen, and clumped in the middle and deep reticular dermis
 - *Course*: decreased lifespan owing to cardiovascular disease
 - *Management*: regular eye exams, cardiology assessment, laboratory tests- CBC, ferritin, serum lipids, urinalysis; aspirin for high risk patients
- Tuberous Sclerosis (Bourneville’s Syndrome, Epiloia)**
- Autosomal dominant or spontaneous mutation
 - Hamartin (*TSC1*, chromosome 9q34); protein function: Together with tuberin, hamartin regulates mTOR-S6K, and cell adhesion through interaction with ezrin and Rho
 - Tuberin (*TSC2*, chromosome 16p13.3); protein function: together with hamartin, tuberin regulates mTOR-s6K and GTPase-activating proteins. Tuberin has a role in cell cycle.
 - **Clinical findings**
 - Triad of *epilepsy*, *low intelligence*, *adenoma sebaceum (epiloia)*
 - Epilepsy: begins during the first year of life
 - Cutaneous manifestations
 - *Hypomelanotic macules*: most common cutaneous manifestation (90% to 98% of patients)
 - *Bilateral facial angiofibromas*: hamartomatous nodules of vascular and connective tissue, in a butterfly pattern over the malar eminences and naso labial folds (80% of children)
 - *Shagreen patch*: connective tissue nevi, usually found on lumbosacral flank
 - *Forehead fibrous plaque*: yellow-brown or flesh-colored plaque, histology shows angiofibroma
 - *Ungual fibroma*: Koenen tumor, connective tissue hamartoma, adjacent to or below nail plate
 - **Other manifestations**
 - *Brain lesions*: cortical tubers (proliferation of glial and neuronal cells), subependymal nodules (hamartomas), subependymal giant-cell tumours, and white matter abnormalities
 - *Dental abnormalities*: dental pits (90% of patients)
 - *Cardiac manifestations*: rhabdomyomas, mainly located in ventricles, recede over time
 - *Renal manifestations*: bilateral angiomyolipomas (70% to 90% of patients), renal cell carcinoma, renal cysts, smooth muscle cell carcinoma
 - *Ocular manifestations*: retinal hamartomas (40% to 50% of patients), mulberry lesions are composed of glial and astrocytic fibers
 - *Pulmonary manifestations*: lymphangiomyomatosis (alveolar smooth-muscle proliferation with cystic destruction of lung)
 - *Hepatic manifestations*: rare angiomyolipomas
 - **Diagnosis** requires the presence of two major features, or one major and two minor criteria
 - **Diagnostic criteria for tuberous sclerosis**:
 - **Major features**
 - ▲ Non-traumatic ungual or periungual fibroma; Koenen’s tumor (Fig. 14-6)
 - ▲ Shagreen patch (connective tissue nevus) migration lines (Fig. 14-7)
 - ▲ Hypomelanotic “ashleaf” macules (three or more) (Fig. 14-8)
 - ▲ Facial angiofibromas or forehead plaque pits in dental enamel (Fig. 14-9)
 - ▲ Multiple retinal nodular hamartomas



FIGURE 14-6 Koenen tumors in tuberous sclerosis complex. (Reprinted with permission from Wolff, K et al: *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)



FIGURE 14-7 Shagreen patch in tuberous sclerosis. (Reprinted with permission from Wolff K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- ▲ Cortical tuber
- ▲ Subependymal nodule
- ▲ Subependymal giant-cell astrocytoma
- ▲ Cardiac rhabdomyoma, single or multiple
- ▲ Lymphangiomyomatosis, renal angiomyolipoma, or both
- Minor features
 - ▲ Multiple, randomly distributed
 - ▲ Hamartomatous rectal polyps
 - ▲ Bone cysts
 - ▲ Cerebral white matter radial
 - ▲ Gingival fibromas
 - ▲ Non-renal hamartoma



FIGURE 14-8 Ash-leaf macules. (Reprinted with permission from Wolff K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)



FIGURE 14-9 Facial angiofibromas. (Reprinted with permission from Wolff K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- ▲ Retinal achromic patch
- ▲ Confetti-like skin lesions
- ▲ Multiple renal cysts
- Management: electroencephalography, cranial MRI, genetic testing, echocardiography, renal ultrasonography, chest computed tomography, ophthalmic examination

Buschke-Ollendorf Syndrome (Dermatofibrosis Lenticularis)

- Autosomal dominant
- LEMD3 gene
- Increased desmosine and elastin in skin
- Clinical findings
 - Dermatofibrosis lenticularis disseminata: symmetrical skin colored to yellowish grouped papules and nodules forming plaques; localized on the trunk: sacrolumbar region and extremities
 - Osteopoikilosis: radiopaque round or oval spots in the epiphyses and the metaphyses of the long bones, pelvis and the bones of hands and feet, no increased fracture risk
- Histology: thickened collagen fibers in the dermis; fragmented elastic fibers
- Prognosis: normal lifespan

Focal Dermal Hypoplasia (Goltz Syndrome)

- X-linked dominant (lethal in males)
- Mutations in PORCN and Wnt signaling may be implicated
- Clinical findings
 - *Cutaneous anomalies*: atrophic, linear hypo- or hyperpigmented patches, telangiectatic streaks in Blaschko's lines, fat herniations through dermal defects (focal dermal hypoplasia), papillomas on lips, perineum, axilla, absent/dystrophic fingernails, sparse, brittle hair
 - *Skeletal anomalies*: syndactyly with "lobster claw" deformity, ectrodactyly, polydactyly, absence or hypoplasia of digits, scoliosis, skeletal asymmetry, clavicular dysplasia, spina bifida occulta, osteopatha striata (linear striations primarily in the long bones)
 - *Dental anomalies*: hypodontia, oligodontia, microdontia, enamel fragility, dysplasia, malocclusion
 - *Eye findings*: microphthalmia, bilateral coloboma of the iris, ectopia lentis, strabismus, anophthalmia
 - *Other manifestations*: mild mental retardation, hearing defects, horse shoe kidneys, hernias: inguinal, umbilical, epigastric
 - *Cardiac anomalies*: cardiac tumors, congenital heart disease (truncus arteriosus)
- Course: normal lifespan

Lipoid Proteinosis (Urbach-Wiethe Syndrome, Hyalinosis cutis et mucosae)

- Autosomal recessive
- ECM1
- Clinical findings
 - Dental anomalies and loss of teeth early
 - *Cutaneous manifestations*: eyelid with beaded papules (appear as a string of pearls), yellow waxy papules on skin, lips, palate, generalized skin thickening, hyperkeratosis at sites of trauma (hands, elbows, knees), pock-like or acneiform scars, infiltration of mucous membranes (pharynx, tongue, soft palate, lips) leading to difficulty in breathing, hoarseness
 - *CNS manifestations*: temporal and hippocampal sickle or bean-shaped calcifications
- Histology: dermal deposition of diastase-resistant PAS positive hyaline material
- Treatment: CO₂ laser treatment of vocal cords and eyelid papules; etretinate, penicillamine

Aplasia Cutis Congenita

- Autosomal dominant, autosomal recessive, or sporadic
- Clinical findings
 - Localized absence of epidermis, dermis, subcutis, bone or dura
 - Well-demarcated erosions/ulcerations; 65% occur on scalp, 25% of cases are found on the trunk or limbs
 - May present as an isolated defect or be combined with congenital malformations (abnormal limbs, dysraphism, facial cleft, abnormalities of the eyes, digestive tract, heart, neurological malformations), chromosome anomalies (Down's syndrome, 4 p-syndrome), or other disorders such as bullous epidermolysis and pyloric stenosis.
 - Adams-Oliver syndrome (AOS): most commonly of the scalp and skull, and terminal transverse limb defects, congenital heart disease.
- Treatment: wound care, most lesions heal with scar formation

PREMATURE AGING AND PHOTSENSITIVE DISORDERS

Progeria (Hutchinson-Gilford Progeria Syndrome)

- Autosomal dominant
- Lamin A defect (LMNA): produces some normal lamin A and some mutated lamin A (progerin).
- Clinical findings
 - Premature signs of aging: alopecia (including scalp and eyebrows), prominent scalp veins

and forehead, classical facial features including micrognathia (small jaw), prominent eyes and a convex nasal profile (beak-like nose), and circumoral cyanosis

- High-pitched voice
- Loss of subcutaneous fat, muscle wasting
- Cutaneous: mottled hyperpigmentation, sclerodermoid changes on lower extremities
- Dystrophic teeth
- Skeletal manifestations: frequent osteolysis, limited joint mobility (contractures), coxa valga, and shortened clavicles, short stature
- Cardiovascular and cerebrovascular diseases: myocardial ischemia and infarction as well as stroke; angina, chronic congestive heart failure, or transient ischemic attacks
- Course: premature death in teens owing to atherosclerotic complications (angina, MI, CHF, CVA)

Werner Syndrome (Progeria Adultorum, Progeria of the Adult, Pangeria)

- Autosomal recessive
- *WRN* gene (*RECQL2*) encodes DNA helicase
- Decreased growth of skin fibroblasts
- Increased urinary hyaluronic acid (abnormal glycosaminoglycan metabolism)
- Clinical findings
 - Premature aged appearance: muscle wasting, progressive alopecia, premature graying of hair, mild diabetes, cataract formation, loss of subcutaneous fat, dermal atrophy with resulting tight, shiny skin on face and extremities (scleroderma-like changes), poikiloderma, leg ulcers, soft tissue and blood vessel calcifications, arteriosclerosis, mesenchymal tumors
 - Short stature, osteoporosis, osteoarthritis
 - Ocular: posterior subcapsular cataracts
- Course: premature death in fourth decade owing to malignancy or atherosclerosis

Acrogeria (Grotton Syndrome, Familial Acromicria)

- Autosomal recessive
- Onset occurring up to age 6 years
- Clinical findings
 - Cutaneous atrophy and subcutaneous wasting of the face and extremities
 - Hair unaffected

Rothmund-Thomson Syndrome (Poikiloderma Congenitale)

- Autosomal recessive
- *RECQL4* (RecQ DNA helicase); chromosome 8q24.3
- Onset ages of 3 to 6 months

- Clinical findings
 - Cutaneous manifestations: poikiloderma, photosensitivity, scaling, hyperkeratosis, and disturbance of hair growth.
 - Other abnormalities include: cataracts, congenital bone defects, soft tissue contractures, and osteogenesis imperfect, short stature, small skull, hypogonadism, dystrophic nails and teeth
 - Malignancies: osteosarcoma, fibrosarcoma, and nonmelanoma skin cancers

Cockayne Syndrome

- Autosomal recessive
- Type 1: CSA (also called CNK1 or excision-repair cross-complementing group 8, *ERCC8* gene); chromosome 5q12-q13
- Type 2: CSB (also called *ERCC6* gene); chromosome 10q11, 80% of cases
- Deficiency in transcription-coupled nucleotide excision repair (TC-NER)
- Increased sister chromatid exchanges
- Clinical findings
 - *Cutaneous manifestation*: photosensitive skin eruption (may affect any sun-exposed area). Pruritus, no increased risk of cutaneous or visceral malignancy
 - *Typical facies*: progeroid, with sparse, dry hair, facial lipoatrophy, large ears, and a thin nose
 - *Ocular findings*: poor pupillary dilatation, enophthalmos (due to loss of subcutaneous fat), optic nerve hypoplasia, and retinal pigmentation, “salt and pepper,” retinal pigmentation, cataracts (15% of patients)
 - *Musculoskeletal, central nervous, and genitourinary systems*: kyphoscoliosis and flexion deformities of the hips, knees, and ankles; abnormal gait, developmental delay and mental retardation, microcephaly, large hands and feet
 - *Sensorineural hearing impairment*
 - *Genitourinary*: Approximately one-third of boys have undescended testes and girls frequently exhibit menstrual irregularities
 - *Cockayne syndrome I (CS-I)*, classic Cockayne syndrome, symptoms begin after the first year of life, survive into adolescence and early adulthood
 - *Cockayne syndrome II (CS-II)/Pena-Shokeir type*: exhibit intrauterine growth retardation, poor postnatal growth, congenital cataracts or early structural eye abnormalities, and severe and more rapidly progressive neurologic impairment.
 - CS is frequently associated with xeroderma pigmentosum (XP) and trichothiodystrophy (TTD): these disorders exhibit sensitivity to ultraviolet (UV) light and defects in nucleotide excision repair (NER)

- Treatment: supportive: photoprotection, physical therapy, and optimizing nutrition; genetic counseling

Bloom Syndrome

- Autosomal recessive
- *BLM* gene (*RECQL3*) encodes a DNA helicase, chromosome 15
- Chromosomal instability, increased rate of sister chromatid exchange
- Increased incidence in Ashkenazi Jews
- Clinical findings
 - Onset in infancy
 - Cutaneous findings: erythema, telangiectasias in butterfly distribution, cheilitis, café au lait macules
 - Short stature; characteristic facies
 - High-pitched voice, hypogonadism, infertility
 - Malignancy: 20% have leukemia, lymphoma, or colon cancer
 - Other medical problems: type 2 diabetes mellitus, chronic lung disease, immune deficiency with recurrent gastrointestinal and respiratory infections, abnormal liver function tests

Seckel Syndrome (Microcephalic Primordial Dwarfism)

- Autosomal recessive
 - Mutation of pericentrin (*PCNT*) gene, functions to anchor both structural and regulatory proteins in the centrosome
- Clinical findings
 - Bird-headed dwarfism: growth retardation, microcephaly, micrognathia, beak-like nose, dwarfism
 - Other manifestations: mental retardation, trident hands, skeletal defects, hypodontia, hypersplenism, premature graying

SYNDROMES WITH MALIGNANCY

Dyskeratosis Congenita (Zinsser-Engman-Cole Syndrome)

- *X-linked recessive* (xq28), gene mutation *DKC1*; encodes dyskerin- a nucleolar protein found in small nucleolar RNA protein complexes.
- *Autosomal dominant*: milder spectrum of disease; gene mutation of human telomerase RNA component (*hTERC*); responsible for synthesizing telomeric DNA repeats; the mutation results in genomic instability and widespread cell death
- *Autosomal recessive*: unknown genetic mutation
- *Hoyerall-Hreidearsson syndrome*: severe variant of DC, multisystem disorder that develops in the neonatal period and infancy; severe growth retardation of perinatal onset, bone marrow failure,

immunodeficiency, cerebellar hypoplasia and microcephaly.

- Clinical findings
 - Triad of nail dystrophy, increased skin pigmentation, and mucosal leukoplakia
 - *Mucocutaneous features*:
 - Poikiloderma neck, face, chest and arms (90% of patients)
 - Dystrophic nails (90% of patients) with longitudinal ridging and splitting with complete nail loss.
 - Mucosal leukoplakia (80% of patients): lingual mucosa, buccal mucosa, palate, and tongue (most commonly affected). Increased risk of malignancy at leukoplakia sites (35% of patients)
 - Other findings: cutaneous atrophy, hyperhidrosis of the palms and soles, telangiectasias, cracking, fissuring, bullae formation, loss of dermal ridges, hair tufts with keratotic plugs on the limbs and keratinized basal cell papillomas, alopecia, amyloidosis
 - *Non-mucocutaneous features*:
 - Pulmonary disease (20% of patients)
 - Ophthalmic manifestations: epiphoria due to nasolacrimal duct blockage, conjunctivitis, blepharitis, pterygium formation, ectropion, strabismus, cataracts and optic atrophy.
 - Skeletal manifestations: (20% of patients): mandibular hypoplasia, osteoporosis, abnormal bone trabeculation, avascular necrosis and scoliosis
 - Dental abnormalities: leukoplakia, hyperpigmentation, periodontal disease, hypocalcified teeth, taurodontism
 - Genitourinary abnormalities: hypoplastic testes, hypospadias, phimosis, urethral stenosis, horseshoe kidneys
 - Gastrointestinal abnormalities: esophageal webs causing dysphagia, hepatomegaly, cirrhosis
 - Neurological abnormalities: altered mental status, learning difficulties, peripheral neuropathy
 - Other abnormalities: microcephaly, intracranial calcification, deafness, , and choanal atresia. Bone marrow failure resulting in peripheral cytopenias (75% of patients develop pancytopenia, responsible for death in 70% of patients).
- Course: death in third to fourth decade due to malignancy (usually SCC), gastrointestinal bleed, or infection

Xeroderma Pigmentosa

- Multigenic, multiallelic, autosomal recessive disease

TABLE 14-14 Xeroderma Pigmentosa Features and Mutations

Complementation Group	Mutation	Features
A	XPA	Neurologic abnormalities Most common in Japan DeSanctis-Cacchione syndrome is subtype
B	ERCC3	Xeroderma pigmentosum–Cockayne syndrome complex (XP/CS)
C	XPC	Most common in USA No neurologic abnormalities
D	ERCC2	DNA helicase defect XP/CS, trichothiodystrophy (XP/TTD), cerebro-ocular-facial syndrome (COFS)
E	DDB2	Mild disease, no neurologic changes
F	ERCC4	Mild disease, no neurologic changes
G	ERCC5	Neurologic symptoms only, XP/CS
Variant	XPV POLH	No neurologic abnormalities

**FIGURE 14-10** Xeroderma pigmentosa. (Courtesy of Dr. Joy Kunishige.)

- Eight complementation groups: (XP-A to XP-G)-associated with defects in nucleotide excision repair (NER), (XP variant form, XP-V)-affects the ability to replicate DNA templates carrying unrepaired DNA damage (Table 14-14)
- Clinical findings
 - XP-A: most profound DNA repair defect with minimal repair activity and neurological symptoms commonly occurring
 - XP-C: severe skin lesions, rare neurological symptoms

- *Ocular symptoms* (80% of patients) include photophobia, conjunctivitis, corneal vascularization, and opacification; malignant tumors may also arise
- *Mucocutaneous manifestations* (Fig. 14-10): skin appears prematurely aged, increased incidence of actinic keratosis, keratoacanthoma, squamous cell carcinoma, basal cell carcinoma, melanoma beginning in childhood; poikiloderma
- *Neurologic manifestations*: progressive cognitive deterioration mainly in complementation groups A, D and G: sensorineural deafness, spasticity, ataxia, hyporeflexia
- *DeSanctis-Cacchione syndrome*: subtype mainly associated with XPA, distinguished by severe neurologic disease, dwarfism, and immature sexual development
- Prognosis: two-thirds die by third decade
- Treatment
 - Aggressive avoidance of sun exposure
 - High-dose oral isotretinoin
 - Excision of cutaneous malignancies
 - Imiquimod 5% cream, 5-fluorouracil cream
 - Skin screenings every 3 months
 - Ophthalmologic evaluation

Muir-Torre Syndrome (Fig. 14-11)

- Autosomal dominant disorder characterized by the combination of sebaceous gland tumors of the skin and internal malignancies
- Subtype of hereditary nonpolyposis colorectal cancer syndrome (HNPCC, also called Lynch syndrome)



FIGURE 14-11 Muir-Torre syndrome. (From Freedberg IM et al. *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003.)

- Defect in DNA mismatch repair (MMR) genes
 - Most often *MSH2* located on chromosome 2p
 - Sometimes *MLH1* located on chromosome 3p
- Presents in fifth to sixth decade
- Diagnostic criteria
 - Group A: sebaceous adenoma, sebaceous epithelioma, sebaceous carcinoma, keratoacanthoma
 - Group B: visceral malignancy
 - Group C: multiple keratoacanthomas, multiple visceral malignancies, family history of Muir-Torre syndrome
 - Diagnosis requires: criterion from group A and group B, or all three from group C
- Clinical findings
 - Cutaneous tumors: sebaceous tumors: adenomas, hyperplasia, epitheliomas, sebaceous carcinomas; may also present with keratoacanthomas
 - Internal malignancies: adenocarcinoma of the colon is most common cancer; other sites include genitourinary tract, hematologic and breast malignancies have also been reported
 - Treatment: sebaceous adenoma and epithelioma—excision or cryotherapy; sebaceous carcinoma—wide excision, radiotherapy or Mohs surgery; keratoacanthoma—excision

Cowden Syndrome (Multiple Hamartoma Syndrome)

- Autosomal dominant
- *PTEN* defect (phosphate and tensin homolog, also called MMAC1), found on 10q23; the gene defect is also found in Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome (PS), and Proteus-like syndrome
- Presents in second to third decade
- Diagnostic criteria
 - Mucocutaneous lesions alone if
 - > 6 facial papules with > 3 trichilemmomas
 - Cutaneous facial papules and oral mucosal papillomatosis
 - Oral mucosal papillomatosis and acral keratoses
 - 6 or more palmar/plantar keratoses, or
 - 2 major criteria but one must include macrocephaly or Lhermitte-Duclos disease, or
 - 1 major and 3 minor criteria, or
 - 4 minor criteria
 - *Pathognomonic criteria*: facial papules (facial trichilemmomas and papillomatous papules), acral keratoses and oral papillomatosis
 - *Major criteria*: breast cancer, thyroid cancer, macrocephaly, hamartomatous outgrowths of cerebellum (Lhermitte-Duclos disease)
 - *Minor criteria*: thyroid lesions (goiter, adenoma), hamartomatous intestinal polyps, fibrocystic disease of the breast, lipomas, fibromas, genitourinary tumors or malformations, mental retardation (IQ < 75)
- Clinical findings
 - *Mucocutaneous lesions*: facial trichilemmomas, acral keratoses, oral papillomas—found mainly on the buccal and gingival mucosa, where coalescent lesions lead to a characteristic cobblestone-like pattern; other cutaneous lesions: lipomas, xanthomas, vitiligo, neuromas, hemangiomas, lentigines, acanthosis nigricans
 - *Extracutaneous findings*
 - *Breast abnormalities*: fibrocystic breast changes, fibroadenomas
 - *Thyroid abnormalities*: (60%) goiter, benign adenoma, thyroglossal duct cyst, hyper- or hypothyroidism, thyroiditis

- *Gastrointestinal abnormalities*: polyps have low malignant potential, diverticula, hepatic hamartomas
- *Urogenital abnormalities*: ovarian cysts, uterine leiomyomas, hydrocele and varicocele in males, hypoplastic testes, vulvar and vaginal cysts
- *Ocular abnormalities*: cataracts, angioid streaks, myopia
- *Nervous system abnormalities*: neuromas, neurofibromas, meningiomas
- *Skeletal abnormalities*: adenoid facies, bone cysts, craniomegaly, high arched palate, kyphoscoliosis, pectus excavatum, rudimentary sixth digit, syndactyly
- *Internal malignancy*: breast adenocarcinoma (at least 20% of cases); follicular thyroid adenocarcinoma (7%), endometrial cancer, adenocarcinoma of the colon, hepatocellular carcinoma
- *Lhermitte-Duclos disease*: variant with cerebellar hamartomas and ataxia
- **Diagnosis and evaluation**
 - Baseline studies: thyroid function tests, thyroid scanning, complete blood count, urinalysis, mammography and chest radiography.

Gardner Syndrome

- Autosomal dominant; 25% of cases occur due to spontaneous mutations.
- Adenomatosis polyposis coli (APC) gene, a tumor suppressor gene; linked to 5q21-q22
- Defect also found in familial adenomatous polyposis (FAP)
- Promotes destruction of β -catenin: component of a transcription factor complex
- **Clinical findings**
 - *Gastrointestinal manifestations*: polyposis of colon by second to fourth decade; most develop colon or rectal cancer
 - *Skeletal manifestations*: osteomas of the skull and jaw (50% of patients), supernumerary teeth
 - *Cutaneous manifestations*: epidermoid cysts of head and neck (66% of patients), fibromas, neurofibromas, lipomas, leiomyomas, pigmented skin lesions.
 - *Tumors*: desmoid, fibromas, hepatoblastoma
 - *Ocular manifestations*: congenital hypertrophy of the retinal pigment epithelium (CHRPE)
 - *Other manifestations*: papillary thyroid cancer, meningiomas, hepatoma, hepatoblastoma, fibromas, leiomyomas, lipomas, biliary and adrenal neoplasms, osteosarcoma, chondrosarcoma
- **Diagnosis**: DNA analysis
- **Treatment**: colonoscopies, prophylactic colectomy, high fiber diet, screen family members with large



FIGURE 14-12 Peutz-Jeghers syndrome. (Courtesy of Dr. Asra Ali.)

bowel and upper GI surveillance, as well as thyroid and possibly hepatic surveillance.

Peutz-Jeghers Syndrome (Periorificial Lentiginosis) (Fig. 14-12)

- Autosomal dominant or sporadic
- *STK11* gene (serine/threonine protein kinase, *LKB1*) tumor suppressor gene; mapped to chromosome 19p13.13
- Presents in childhood
- **Clinical findings**
 - *Cutaneous findings*: lentiginos on mucosa, periorificial skin, palms, digits; present at birth; lesions on the skin and lips often fade after puberty, while intraoral lesions persist
 - *Gastrointestinal findings*: hamartomatous polyps (more common in small intestine) may cause bleeding, pain, intussusception, obstruction; adenocarcinoma
 - *Genitourinary findings*: ovarian neoplasm—most common sex cord tumor with annular tubules (SCTAT), mucinous epithelial ovarian tumor, serous tumor and ovarian mature hamartoma; endometrial adenocarcinoma, and adenoma malignum of the cervix
 - *Endocrine findings*: gynecomastia due to calcified Sertoli cell testicular tumors
 - *Other findings*: breast cancer (usually ductal), pancreatic cancer
- **Diagnosis**: monitor with colonoscopy, polypectomy
- **Course**: normal lifespan if malignancy detected early

Multiple Endocrine Neoplasia IIa (Sipple Syndrome)

- Autosomal dominant
- Receptor tyrosine kinase (*RET*) protooncogene; activation of Ret protein and results in hyperplasia of target cells—such as C cells (clear large cells in a peri- or parafollicular location; precursor lesion for medullary thyroid carcinoma [MTC]) in the thyroid gland and chromaffin cells in adrenal glands.
- Clinical findings
 - Macular or lichen amyloidosis
 - Hyperparathyroidism with parathyroid hyperplasia (20% of cases) or adenoma
 - Thyroid hyperplasia or medullary thyroid carcinoma (MTC)
 - Pheochromocytoma, bilateral in 70% of cases; age at onset is approximately 40 years; patients present with hypertension, sweating, palpitations and tachycardia, nausea, vomiting, polyuria, polydipsia
- Diagnosis: *RET* germline mutation testing
- Laboratory work up: calcitonin levels, urine catecholamine; plasma free and urinary fractionated metanephrines
- Imaging studies: pheochromocytomas: CT scan, MRI, metaiodo-benzylguanidine (MIBG) scanning; OctreoScan imaging, positive emission tomography (PET).
- Treatment: total thyroidectomy with radical lymph-node dissection (patients 5 years or older with *RET* mutation); pheochromocytomas: surgical excision

Multiple Endocrine Neoplasia IIb (Multiple Neuroma Syndrome)

- Autosomal dominant
- Receptor tyrosine kinase (*RET*) mutations; protooncogene
- Chromosomal locus 10q11
- Clinical findings
 - Mucosal neuromas may result in thickened lips, eyelid eversion
 - Medullary thyroid carcinoma; aggressive, occurs in childhood
 - Pheochromocytoma
 - Marfanoid habitus
 - Adrenomedullary hyperplasia; multifocal and often bilateral
 - Gastrointestinal ganglioneuromatosis with megacolon; constipation or diarrhea
- Laboratory work up: calcitonin levels, urine catecholamine; plasma free and urinary fractionated metanephrines
- Imaging studies: pheochromocytomas: CT scan, MRI, metaiodo-benzylguanidine (MIBG) scanning;

OctreoScan imaging, positive emission tomography (PET).

- Course: normal lifespan with early detection and treatment of thyroid carcinoma
- Treatment: total thyroidectomy with radical lymph-node dissection (patients 5 years or older with *RET* mutation); pheochromocytomas: surgical excision

Carney Complex

- Autosomal dominant; mutations in the *PRKAR1A* gene; encodes the R1a regulatory subunit of protein kinase A.
- The following syndromes are now included under Carney complex:
 - LAMB (lentiginos, atrial myxomas, mucocutaneous myxomas, and blue nevi)
 - NAME (nevi, atrial myxoma, myxoid neurofibroma, and ephelides)
- Clinical findings: pituitary adenoma, Sertoli-cell tumors, thyroid nodules, cardiac myxomas (accounts for 7% of all cardiac myxomas)
- Cutaneous findings: skin myxomas, melanotic schwannomas, lentiginos (common areas: face, trunk, lips)
- Imaging studies: echocardiography
- Treatment: surgical excision of intracardiac myxomas

DISORDERS ASSOCIATED WITH IMMUNODEFICIENCY

Wiskott-Aldrich Syndrome (WAS)

- X-linked recessive
- WAS gene, Xp11; genetic defect in Wiskott-Aldrich syndrome protein (WASp)
- Decreased sialophorin (CD43) on surface of lymphocytes
- Impaired T- and NK-cell function
- Clinical findings
 - Atopic dermatitis with secondary infection, allergies, asthma
 - Recurrent bacterial infections
 - Thrombocytopenia, petechiae, bloody diarrhea
 - Increased IgA, IgD, and IgE, but decreased IgM
- Course: death from infection, hemorrhage, or lymphoreticular malignancy
- Laboratory studies
 - serum immunoglobulin levels, complete blood cell count
- Imaging studies
 - Computed tomography: splenomegaly, rule out malignancy. Evaluation of intracranial bleeding, sinus or pulmonary infections.

- Treatment: topical steroids and moisturization for eczema, intravenous immunoglobulin and/or steroids for thrombocytopenia; bone marrow transplantation

Chronic Granulomatous Disease

- X-linked recessive, sometimes autosomal recessive
- Mutations in nicotinamide dinucleotide phosphate (NADPH) oxidase subunits (eg. gp91^{phox} subunit of cytochrome b, or p47^{phox})
- Deficient killing of phagocytised organisms
- Clinical findings
 - Pyodermas, perianal abscesses, and perioral ulcers
 - Pneumonia and emphysema
 - Osteomyelitis with *Serratia*
 - Hepatosplenomegaly with granulomas
 - Nitroblue tetrazolium assay abnormal (abnormal leukocytes unable to reduce dye and make blue color)
- Treatment includes interferon-gamma

Hyper-immunoglobulin E Syndrome

- Autosomal dominant
- Chromosome 4q
- Increased levels of IgE
- Clinical findings
 - Eczematous rash
 - Cold abscesses with *Staphylococcus*, *Streptococcus* or *Candida*
 - Sinopulmonary infections with *Staphylococcus*, *H. Influenza*, or fungus
 - Osteopenia with bone fractures and scoliosis
 - Retention of primary teeth and other dental anomalies
 - Job syndrome is a subgroup with hyperextensible joints.

Severe Combined Immunodeficiency

- X-linked recessive, sometimes autosomal recessive
- Defect in γ chain of IL-2 receptor, adenosine deaminase, or JAK 3 pathway
- Impaired T-cells, may also affect NK- and B-cells
- Clinical findings
 - Absent thymus on x-ray, lack tonsillar buds
 - Recurrent infections with *Candida*, *Staphylococcus*, and *Streptococcus*
 - Pneumonias with *Pneumocystis carinii*, Parainfluenza, or *Cytomegalovirus*
 - Chronic viral diarrhea, malabsorption, and failure-to-thrive
 - Graft-versus-host reaction to in utero maternal lymphocytes
 - Must irradiate blood products before transfusion and avoid live vaccines
 - Omenn syndrome: severe variant with failure-to-thrive, alopecia, and erythroderma; secondary to RAG 2 gene mutation

Leukocyte Adhesion Deficiency (LAD)

- Autosomal recessive
- CD18 gene (part of an integrin)
- Impaired leukocyte mobilization
- Clinical findings
 - Gingivitis can lead to loss of teeth
 - Poor wound healing, so wounds become large ulcers
 - Delayed separation of umbilical cord
 - Differentiate this from Type II LAD which also has mental retardation and short stature; defect in GDP-fucose biosynthesis

DISORDERS WITH CHROMOSOME ABNORMALITIES

Down Syndrome (Trisomy 21)

- Mainly sporadic secondary to nondisjunction at chromosome 21
- Presents at birth
- Clinical findings
 - Single palmar crease
 - Nuchal skin folds
 - Syringomas
 - Elastosis perforans serpiginosa
 - Xerosis and lichenification with age
 - Alopecia areata
 - Flat nasal bridge, short broad neck, epicanthal folds, small mouth with protruding scrotal tongue
 - Mental retardation and seizures
 - Congenital heart disease
 - Duodenal atresia
 - Acute myelogenous leukemia
- Course: increased infant mortality secondary to congenital heart defects and neoplasms

Turner Syndrome (Gonadal Dysgenesis, Ullrich-Turner)

- Sporadic loss of one X chromosome (XO monosomy)
- Some cases demonstrate mosaicism
- Clinical findings
 - Dermatologic findings: melanocytic nevi, koilonychia, increased keloids, webbed neck
 - Low-set hairline, patchy alopecia
 - Triangular facies, short stature, shield chest with wide-set nipples, cubitus valgus
 - Primary amenorrhea, infertility
 - Mental retardation
 - Horseshoe kidneys
 - Coarctation of aorta
- Treatment: estrogen replacement, treatment of congenital anomalies

Noonan Syndrome

- Autosomal dominant
- PTPN11 gene encoding protein tyrosine phosphatase SHP2, recently SOS1 and RAF1 mutations reported
- Clinical findings
 - Resemble Turner syndrome with short stature, webbed neck, low posterior hairline, cubitus valgus
 - Cryptorchidism
 - Cardiac malformations (pulmonic stenosis)
 - Lymphedema
 - Tendency for keloid formation
- Treatment: correction of cardiac defects

Klinefelter Syndrome

- 47,XXY
- Decreased serum testosterone
- Clinical findings
 - Hypogonadism, gynecomastia
 - Tall with low hairline
 - Sparse body hair
 - Mental retardation, psychiatric problems in one-third of patients
 - Thrombophlebitis, leg ulcers
 - Risk of gonadal tumors, breast cancer
- Treatment: testosterone replacement and wound care

QUIZ**Questions**

1. Type VIIC (dermatospraxis) Ehlers-Danlos syndrome is caused by a problem with collagen formation at which site?
 - A. Nucleus
 - B. Ribosome
 - C. Golgi lumen
 - D. Extracellular space
2. Lamellar ichthyosis is characterized by which of the following?
 - A. Widespread bullae at birth, palmoplantar keratoderma later
 - B. Superficial blistering and molting, followed by flexural hyperkeratosis
 - C. Collodion baby followed by large platelike scales
 - D. Migratory geographic patches of erythema that stabilize after puberty
3. The defect in Louis-Bar syndrome involves:
 - A. DNA repair
 - B. Tumor suppressor
 - C. Developmental error
 - D. TGF-beta receptor
4. The defect in the syndrome marked by clumped melanosomes in the fetal hair shaft, silvery hair, abnormal platelets, and recurrent infections involves:
 - A. Tyrosinase
 - B. P gene
 - C. Melanosome transfer
 - D. C-kit
5. Aplasia cutis congenital can be associated with all of the following EXCEPT:
 - A. Otherwise healthy newborn
 - B. Limb hypoplasia
 - C. Lung hypoplasia
 - D. Epidermolysis bullosa
6. Your patient presents with telangiectasias, photosensitivity, acral keratoses, alopecia, and cataracts since age 5. You counsel your patient that he has risk for:
 - A. Squamous cell carcinoma and sarcoma
 - B. Leukemia and frequent infections
 - C. Hypertension and vascular malformations
 - D. Neurologic degeneration including deafness
7. If you suspect a patient has Neimann-Pick disease, you might examine the skin to look for what lesion?
 - A. Melanoma
 - B. Café-au-lait macules
 - C. Xanthomas
 - D. Cherry red spots
8. Some porphyrias can have acute attacks precipitated by various drugs, infections, alcohol, dieting, and pregnancy. What symptoms suggest an acute attack?
 - A. Photosensitivity and fluorescent urine
 - B. Abdominal pain and confusion
 - C. Gallstones and blisters
 - D. Hemolytic anemia and liver cancer
9. Because rapamycin inhibits mTOR activity, it has been used to shrink tumors associated with which syndrome?
 - A. Gorlin's syndrome
 - B. Familial cylindromatosis
 - C. Neurofibromatosis
 - D. Tuberous sclerosis
10. Coloboma is associated with all of the following EXCEPT:
 - A. Goltz's syndrome
 - B. Bloch-Sulzberger's syndrome
 - C. CHIME (neuroectodermal) syndrome
 - D. Urbach-Wiethe syndrome

Answers

1. D. This type of Ehlers-Danlos syndrome involves a mutation in the ADAM-TS2 gene, or N-peptidase gene. N-peptidase cleaves the N-terminus of collagen Type I in the extracellular space, where tropocollagen is formed to then be incorporated into mixed fibrils.
2. C. Unlike many other ichthyoses, lamellar ichthyosis persists and remains severe past childhood. Characteristic large, squarish, “dry riverbed” scales are most prominent in the flexures.
3. A. The ATM gene encodes a phosphatidylinositol-3-kinase-like protein that is involved in DNA repair. Ataxia-telangiectasia, or Louis-Bar syndrome, is neurodegenerative and immune system disorder associated with infections and malignancies, particularly lymphomas and leukemias.
4. C. Chediak-Higashi syndrome is caused by a mutation in the LYST gene, which encodes a trafficking protein. Decreased melanosome transfer results in clumped melanosomes visible in the medulla of fetal hair shafts, useful for diagnosis.
5. C. Aplasia cutis congenita (ACC) is associated with multiple abnormalities listed above except for lung hypoplasia. The association of epidermolysis bullosa with ACC is called Bart’s syndrome. The association of ACC with cutis marmorata telangiectatica congenita and limb abnormalities is called Adams-Oliver syndrome.
6. A. Rothmund-Thomson syndrome (poikiloderma congenitale) patients have acral verrucous keratoses that can evolve into squamous cell carcinomas. Patients also have rare osteosarcoma and fibrosarcoma. The above findings are related to the RecQL4 helicase defect.
7. C. Xanthomas on the face and upper extremities can be seen in Niemann-Pick disease. Cherry red spots are located in the fovea and would not be visible on the skin.
8. B. Acute attacks occur when hemoglobin or cytochromes, the end products of the porphyria pathway, are depleted. Acute attacks manifest with abdominal pain, peripheral neuropathy, confusion, seizure, tachycardia, and hypertension. Treatment includes glucose, hematin, carbohydrates, and hormones.
9. D. Normally, hamartin and tuberlin associate with each other to inhibit Rheb. Rheb in turn increases mTOR signaling which results in cell growth. Tuberous sclerosis 1 and 2 result from defects in hamartin or tuberlin, respectively. Patients with tuberous sclerosis have increased mTOR, which can be inhibited by the drug rapamycin.
10. D. Coloboma is a gap in a structure of the eye due to incomplete development, and is associated with

Goltz’s syndrome, Bloch-Sulzberger’s syndrome, and CHIME syndrome. Sickie-shaped beanbag calcifications in the hippocampus and eyelid (“string of pearls”) are associated with Urbach-Wiethe syndrome (lipoid proteinosis).

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PEDIATRIC DERMATOLOGY

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DISORDERS OF PIGMENTATION

Mongolian Spot (Fig. 15-1)

- Presentation
 - Blue-gray patches present at birth or early infancy
 - Usually buttocks, lumbosacral back
 - Common in black, Hispanic, and Asian races
 - Color due to Tyndall effect (scattering of light as it strikes dermal melanin)
- Course
 - Usually resolves by early to late childhood
 - Extensive Mongolian spots (dermal melanocytosis) with dorsal/ventral distribution, indistinct borders, and persistent and/or “progressive” behavior may be a sign of underlying lysosomal storage disease (most commonly GM1 gangliosidosis type 1 and Hurler disease)

Nevus of Ota (Fig. 15-2)

- Also known as oculodermal melanocytosis, nevus fuscoceruleus ophthalmomaxillaris
- Presentation
 - Unilateral bluish gray discoloration of facial skin
 - Affects region supplied by trigeminal nerve V_1 and $V_2 \pm$ ipsilateral sclera
 - Congenital or acquired by second decade
 - More common in black or Asian races, females
- Treatment: pigmented lesion lasers
- Course
 - Persists; both this and nevus of Ito may increase in size/intensity over time
 - Ocular involvement: risk of glaucoma

Nevus of Ito (Fig. 15-3)

- Also known as nevus fuscoceruleus acromiodeltoides
- Presentation: similar to nevus of Ota but localized to unilateral shoulder, lateral neck, scapula, and/or deltoid
- Course: persists
- Treatment: pigmented lesion lasers

Mosaic Hypopigmentation (Fig. 15-4)

- Includes hypomelanosis of Ito (incontinentia pigmenti acromians), nevus depigmentosus (achromic nevus)
- Presentation
 - Benign, hypopigmented oval or round patches, bands, or swirls
 - May be localized or extensive
 - Arranged along one or more Blaschko lines
 - No preceding vesicular or inflammatory stages
 - Incidence of systemic manifestations highest with most extensive lesions
 - Most commonly CNS, musculoskeletal, and eyes depending on particular chromosome defect and level of mosaicism
- Course: persists

VASCULAR DISORDERS

Blueberry Muffin Baby (Fig. 15-5)

- Presentation
 - Multiple, dark blue to magenta, small, nonblanching papules and macules
 - Present at birth or by first day of life
- Etiology
 - Extramedullary hematopoiesis



FIGURE 15-1 Mongolian spot. (Courtesy of Dr. Adelaide Herbert.)

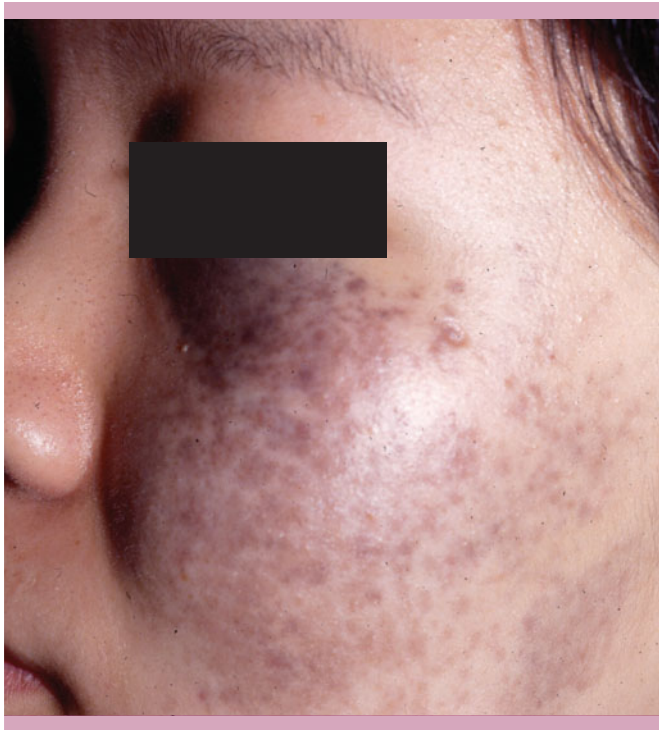


FIGURE 15-2 Nevus of Ota. (Courtesy of Dr. Adelaide Herbert.)

- Associated with congenital infections (TORCH viruses, most commonly cytomegalovirus), hemolytic disease of the newborn, hereditary spherocytosis, twin-twin transfusion syndrome



FIGURE 15-3 Nevus of Ito. (From Weinberg S et al. *Color Atlas of Pediatric Dermatology*, 3rd Ed. New York: McGraw-Hill; 1998, p. 229.)



FIGURE 15-4 Hypomelanosis of Ito. (Courtesy of Dr. Adelaide Herbert.)

- Differential
 - Includes neoplastic-infiltrative disease (lesions typically larger, more nodular, and fewer in number)
 - Neuroblastoma, rhabdomyosarcoma, Langerhans' cell histiocytosis (especially congenital self-healing histiocytosis, also known as Hashimoto-Pritzker disease), congenital leukemia (especially myelogenous)
- Course
 - Skin lesions involute spontaneously in 2 to 6 weeks



FIGURE 15-5 Blueberry muffin baby. (Courtesy of Dr. Denise Metry.)



FIGURE 15-6 Acute hemorrhagic edema of infancy. (Courtesy of Dr. Denise Metry.)

- Evaluation may include complete blood count (CBC), viral cultures, TORCH serologies, Coombs' test; skin biopsy if neoplastic infiltration suspected
- Therapy: directed toward underlying cause

Acute Hemorrhagic Edema of Infancy (Finkelstein's Disease) (Fig. 15-6)

- Presentation
 - Acute form of leukocytoclastic vasculitis
 - Children under 2 years
 - Often history of preceding infection
 - Rapid onset



FIGURE 15-7 Henoch-Schonlein purpura. (Courtesy of Dr. Denise Metry.)

- Fever, edema, and targetoid purpuric lesions on face, ears, distal extremities
- Children generally appear well despite alarming appearance of skin lesions
- Systemic symptoms: renal, joint, gastrointestinal (GI) involvement exceptional (important difference from adult Henoch-Schonlein purpura)
- Course: clinical improvement in 1 to 3 weeks

Henoch-Schonlein Purpura (Anaphylactoid Purpura) (Fig. 15-7)

- Presentation
 - Triad: characteristic skin lesions, abdominal pain, and hematuria
 - Children and young adults
 - Often preceding upper respiratory infection
 - Pink or erythematous papules that become purpuric on extensor extremities, buttocks
 - Develop in crops
- Systemic signs and symptoms
 - Abdominal pain
 - Arthralgias
 - Hematuria
 - Nephritis; rare progressive glomerular disease
- Course
 - Most resolve in 6 to 16 weeks
 - May recur
 - Severe/prolonged disease more common in older children/adolescents
 - Nephritis may manifest up to 3 years after initial onset; important to monitor urinalyses (UAs)
- Treatment: supportive care

Nevus Anemicus (Fig. 15-8)

- Presentation
 - Congenital vascular abnormality, asymptomatic



FIGURE 15-8 Nevus anemicus. (Courtesy of Dr. Denise Metry.)

- Most commonly occurs as a single patch of skin pallor on the trunk
- Localized vascular hypersensitivity to catecholamines
- Catecholamine sensitivity produces increased vasoconstriction and skin pallor
- Diagnosis
 - Diascopy: when pressure is applied to the border of the patch with a clear glass slide; the border between lesion and normal skin disappears
 - Rubbing the affected area causes erythema of the surrounding skin, but the lesion itself remains unchanged
 - Histopathology is normal
- Treatment: none

INFECTIONS

Molluscum Contagiosum (Fig. 15-9)

- Presentation
 - Skin-colored, umbilicated papules
 - Children commonly affected
 - Contagious, with autoinoculation
- Causative organism
 - Pox virus (large DNA virus, 200–300 nm)
- Diagnosis
 - Usually clinical
 - Histology: Henderson-Patterson bodies (cytoplasmic viral inclusion bodies) on path
- Course: Individual lesions last weeks to months; total course may last several months to years
- Treatment
 - Not required because lesions will resolve spontaneously



FIGURE 15-9 Molluscum contagiosum. (Courtesy of Dr. Denise Metry.)



FIGURE 15-10 Eczema herpeticum. (Courtesy of Dr. Denise Metry.)

- Destructive options include cantharidin, curettage, cryotherapy, and topical irritants (retinoic acid, imiquimod)

Eczema Herpeticum (Kaposi's Varicelliform Eruption) (Fig. 15-10)

- Presentation
 - Herpes simplex virus (HSV) infection within preexisting dermatitis (atopic dermatitis, severe seborrheic dermatitis, scabies, bullous disorders)
 - Sudden onset of grouped, uniformly sized vesicles and/or pustules that evolve into crusted erosions
 - Fever, lymphadenopathy, malaise
- Diagnosis
 - Tzanck smear
 - Biopsy
 - Rapid HSV immunofluorescence

- Treatment
 - First episode most serious because of risk of systemic involvement
 - Oral or intravenous acyclovir
- Prognosis
 - Estimated 20% incidence of minor recurrence

Unilateral Laterothoracic Exanthem (Asymmetric Periflexural Exanthem of Childhood)

- Presentation
 - Erythematous papules develop close to a flexure (typically axilla)
 - Papules coalesce and spread to involve the adjacent trunk and extremity
 - Lymphadenopathy common
 - Contralateral involvement occurs occasionally
 - Typically affects children younger than 10 years of age
- Causative organism
 - Etiology unknown
 - Viral cause suspected owing to high incidence of preceding upper respiratory infection or gastroenteritis
- Diagnosis
 - Mainly clinical
 - Histology: lymphocytic infiltrate around eccrine ducts
- Treatment: resolves spontaneously in 2 to 6 weeks

Scabies (Fig. 15-11)

- Presentation
 - Pruritic papules, vesicles, burrows of web spaces, flexures, genitals
 - Often excoriated, impetiginized
 - Spread by close contact
 - Norwegian scabies (Fig. 15-12)
 - Heavily crusted lesions with many mites
 - Immunodeficient, debilitated patients



FIGURE 15-11 Scabies. (Courtesy of Dr. Denise Metry.)

- Nodular scabies (Fig. 15-13)
 - Persistent red nodules; represents hypersensitivity to mites
- Causative organism
 - *Sarcoptes scabiei*
 - Female mite burrows and deposits eggs in stratum corneum
- Diagnosis
 - Clinical
 - Microscopic examination of mite, ova, or feces (scutula) on skin scraping
- Treatment
 - Topical 5% permethrin is treatment of choice (approved down to 2 months of age)
 - For newborn infants or pregnant/nursing women, 6% to 10% sulfur in petrolatum (permethrin is pregnancy category B)



FIGURE 15-12 Norwegian scabies. (From Freedberg IM et al. *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003, p. 2284.)



FIGURE 15-13 Nodular scabies. (Courtesy of Dr. Denise Metry.)



FIGURE 15-14 Staphylococcal scalded skin syndrome. (Courtesy of Dr. Denise Metry.)

Staphylococcal Scalded Skin Syndrome (Ritter's Disease) (Fig. 15-14)

- Presentation
 - Acute onset of tender erythema
 - Rapid development of superficial blistering in periorificial and flexural distribution
 - Subsequent desquamation and fissuring around mouth/eyes produces classic "sad old man" facies.
 - Usually young children (younger than age 2) or adults with predisposing conditions (immunosuppression, renal impairment, overwhelming sepsis)
 - Nikolsky sign present
 - Resolves without scarring
- Causative organism: epidermolytic toxin of *Staphylococcus* phage group II (desmoglein 1 target)
- Diagnosis
 - May isolate *Staphylococcus* from nasopharynx (most common), blood, urine, umbilicus, conjunctivae, (not skin)
 - Histology: shows split at granular layer
- Treatment
 - Penicillinase-resistant penicillin
 - Supportive measures

DERMATOSES

Seborrheic Dermatitis ("Cradle Cap") (Fig. 15-15)

- Presentation
 - Yellowish, scaling dermatitis of scalp



FIGURE 15-15 Seborrheic dermatitis of scalp: infantile type. (From Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th Ed. New York: McGraw-Hill; 2005, p. 51.)

- Greasy, salmon-colored patches on face (central forehead, glabella, eyebrows, nasolabial folds), retroauricular, intertriginous areas
- Blepharitis may be present
- Etiology: possible role of *Pityrosporum ovale* (*Malassezia furfur*)
- Course
 - Generally resolves by 1 year of age
 - Postinflammatory hypopigmentation characteristic of darker-skinned infants
- Treatment
 - Low-potency topical corticosteroids
 - Antiseborrheic shampoos
 - Topical antifungals

Gianotti-Crosti Syndrome (Papular Acrodermatitis of Childhood) (Fig. 15-16)

- Presentation
 - Monomorphic papules or papulovesicles
 - Symmetrically distributed on the face, buttocks, extremities of children (generally starts on thighs/buttocks and then goes to arms and then face)
 - Lesions tend to cluster on knees and elbows
 - Usually spares the trunk
 - Lesions koebnerize



FIGURE 15-16 Gianotti-Crosti syndrome. (Courtesy of Dr. Denise Metry.)

- Constitutional symptoms: low-grade fever, lymphadenopathy, splenomegaly
- Pathology: associated with viral infections: Epstein-Barr virus (most common association in the United States), hepatitis B virus, cytomegalovirus (CMV), respiratory syncytial virus (RSV)
- Course: resolves spontaneously in 3 to 8 weeks
- Treatment: symptomatic

Acropustulosis of Infancy (Infantile Acropustulosis) (Fig. 15-17)

- Presentation
 - Crops of pruritic vesiculopustules on the hands and feet of infants/young children
 - Occurs in crops every 2 to 4 weeks
 - Scabies prep negative
- Etiology: may be reactive to previous scabies exposure
- Pathology: subcorneal and intraepidermal neutrophilic abscesses
- Treatment
 - Potent topical steroids
 - Oral antihistamines
 - Oral erythromycin
 - Dapsone for exceptionally severe cases
- Course: resolves in 1 to 2 years

Transient Neonatal Pustular Melanosis (TNPM)

- Presentation
 - Very superficial vesicles, sterile pustules
 - Seen at birth in up to 4% of healthy, term newborns
 - Rupture with desquamation leaves characteristic residual hyperpigmented macules generally within first 2 days of life
- Pathology: intracorneal and subcorneal neutrophilic spongiosis (few if any eosinophils)
- Treatment
 - Self-limited
 - Postinflammatory pigmentation fades in weeks to months



FIGURE 15-17 Acropustulosis of infancy. (Courtesy of Dr. Adelaide Herbert.)



FIGURE 15-18 Erythema toxicum. (Courtesy of Dr. Denise Metry.)

Erythema Toxicum Neonatorum (ETN) (Fig. 15-18)

- Presentation
 - Common; affects half of full-term newborns
 - “Flea-bitten rash” of few to hundreds of erythematous macules, wheals, papules, and pustules
 - Occurs in the first 24 to 48 hours of life
 - Both TNPM and ETN almost always spare the palms and soles (important distinguishing clinical feature from congenital candidiasis)

- Histology: folliculitis with eosinophils (few neutrophils, no spongiosis)
- Treatment: resolves within 1 to 2 weeks

Lichen Striatus (Fig. 15-19)

- Presentation
 - Linear band of erythematous to flesh-colored papules
 - Develops over several weeks



FIGURE 15-19 Lichen striatus. (Courtesy of Dr. Denise Metry.)

- Follows Blaschko's lines
- Affects children and young adults
- Resolves within 1 to 2 years with postinflammatory hypopigmentation that improves slowly
- Initially may be mildly pruritic
- Pathology
 - Spongiotic or lichenoid dermatitis with necrotic keratinocytes
 - Lymphocytic infiltrate around eccrine coils
- Treatment: topical anti-inflammatories may be useful for pruritus; may hasten resolution of inflammatory lesions

CUTANEOUS NEOPLASMS AND MALFORMATIONS

Epstein's Pearls (Bohn's Nodules)

- Presentation: white to yellow mobile papules at the hard palate (Epstein's pearls) or gum margin (Bohn's nodules) of newborns
- Etiology/pathology: milia
- Treatment
 - No treatment required
 - Resolves within weeks

Pseudoverrucous Papules and Nodules (Fig. 15-20)

- Presentation: shiny, moist, flat-topped erythematous papules of diaper area or surrounding urostomy/colostomy sites
- Etiology/pathology: form of severe irritant contact dermatitis resulting from incontinence, encopresis, severe diaper dermatitis
- Treatment: protection of skin by barrier creams



FIGURE 15-20 Pseudoverrucous papules and nodules. (Courtesy of Dr. Denise Metry.)

Perianal (or Perineal) Pyramidal Protrusion (Fig. 15-21)

- Presentation
 - Triangular-shaped, flesh-colored to erythematous nodule on the perineal median raphe, anterior to the anus
 - More than 90% of cases occur in female infants
 - Average age at presentation: 14 months
- Etiology/pathology: related to constipation, possibly lichen sclerosus et atrophicus
- Course: resolves spontaneously over several months to 1 to 2 years
- Treatment: treating associated constipation may hasten resolution

Nevus Sebaceous of Jadassohn (Fig. 15-22)

- Presentation
 - Congenital hairless, yellow to orange plaque on the scalp (usually round), face, or neck (usually linear)
 - Pebbly, velvety, or cerebriform surface, although often flat at birth
- Etiology/pathology
 - Early: increased numbers of immature sebaceous glands and hair follicles
 - Postpubertal: papillomatosis, hyperkeratosis, and hypergranulosis accompany lobules of sebaceous glands and ectopic apocrine glands
- Course/therapy
 - Prepubertal excision often considered due to low risk of secondary tumor growth later in life
 - Most commonly associated malignant neoplasm: basal cell carcinoma (BCC)
 - Most common benign neoplasm: trichoblastoma

Schimmelpenning's Syndrome

- Presentation: large nevus sebaceous associated with ocular lesions, intracranial masses, mental retardation, seizures, skeletal and/or pigmentary abnormalities

Linear Epidermal Nevus (Fig. 15-23)

- Presentation
 - Verrucous pink to brown papules following Blaschko's lines
 - Generally presents at birth or within first year of life, sometimes later in childhood or adolescence
- Subtypes
 - Systematized epidermal nevus (Fig. 15-24): extensive, bilateral lesions
 - Ichthyosis hystrix/nevus unius lateris: extensive unilateral lesions
 - Inflammatory linear verrucous epidermal nevus (ILVEN)
 - Inflammatory variant with erythema, pruritus
 - Often on an extremity or perineum in girls
- Etiology/histology
 - Hyperplasia of epidermal structures with hyperkeratosis, acanthosis, papillomatosis, some with epidermolytic hyperkeratosis
 - Accompanying parakeratosis and inflammation (with ILVEN)
- Course/therapy
 - Destruction by excision, laser ablation, cryotherapy, dermabrasion, chemical peels, topical retinoids
 - Recurrence is common
 - Pruritus with ILVEN often refractory to treatment



FIGURE 15-21 Perianal pyramidal protrusion. (Courtesy of Dr. Adelaide Herbert.)



FIGURE 15-22 Nevus sebaceous. (Courtesy of Dr. Denise Metry.)



FIGURE 15-23 Linear epidermal nevus. (Courtesy of Dr. Adelaide Herbert.)



FIGURE 15-24 Epidermal nevus. (Courtesy of Dr. Denise Metry.)

Aplasia Cutis Congenita (Fig. 15-25)

- Presentation
 - Well-demarcated ulceration or erosion often with thin, glistening membrane-like surface
 - Present at birth



FIGURE 15-25 Aplasia cutis congenita. (Courtesy of Dr. Denise Metry.)

- Most commonly on vertex
- Seventy percent solitary
- Rare association with other developmental abnormalities
 - Irregular, large, stellate defects of the scalp associated with trisomy 13 and underlying cerebrovascular malformations
 - Large, bilateral, truncal stellate defects associated with fetus papyraceus (placental infarction after the death of a twin fetus) and gastrointestinal atresia
- Etiology/pathology
 - Sporadic or autosomal dominant inheritance with variable penetrance
 - Localized absence of the epidermis, dermis \pm subcutis
- Course/therapy
 - Protection from trauma and infection
 - Most heal within several months, leaving scar
 - MRI/MRA and radiographs for large scalp defects; abdominal imaging for large truncal defects

MASTOCYTOSIS

Solitary Mastocytoma (Fig. 15-26)

- Presentation
 - One to several yellowish to brown nodule(s)
 - Presents within first 6 months of life
 - Often on trunk, upper extremities, neck
 - Darier's sign: when stroked, lesion urticates
 - May develop bullae in infancy
 - Spontaneous regression over several years



FIGURE 15-26 Solitary mastocytoma. (Courtesy of Dr. Denise Metry.)

- Treatment: topical anti-inflammatories can be used for symptoms; otherwise, treatment is unnecessary

Urticaria Pigmentosa

- Presentation
 - Most common form of mastocytosis
 - Develops between 3 and 9 months of life
 - Persistent, pruritic red-brown-yellow macules, papules, or nodules
 - Lesions most common on the trunk
 - Positive Darier's sign
 - Pruritus induced by rubbing, exercise, heat, mast-cell degranulators (EtOH, opiates)
- Etiology: *Hymenoptera* stings or histamine-releasing drugs may rarely cause severe symptoms, anaphylaxis
- Treatment
 - H₁ antagonists for pruritus, urticaria, flushing
 - H₂ antagonists for gastrointestinal symptoms
 - Diarrhea may be controlled with cromolyn (disodium chromoglycate)
 - Calcium channel blockers may inhibit mast cell degranulation
 - Epi-Pen for patients with a history of anaphylaxis
 - Seventy percent of patients markedly improved by adolescence

Diffuse Cutaneous Mastocytosis

- Presentation
 - Rare
 - Presents at birth or within first few weeks of life
 - Skin diffusely infiltrated with mast cells
 - Leathery, orange-peel appearance (*peau d'orange*), especially in flexures

- Widespread spontaneous blistering with erosions and crusts, erythroderma, pruritus
- Etiology: systemic involvement in up to 10% of children (greater in adults)

Systemic Mastocytosis

- Presentation
 - Rare mast cell accumulation in one or more organs other than the skin, especially bone marrow
 - The presence of systemic symptoms does not make the diagnosis of systemic mastocytosis
 - Invasive diagnostic procedures for
 - Patients with hematologic abnormalities
 - Persistent, localized bone pain and severe gastrointestinal symptoms
 - Evidence of hepatic insufficiency
- Signs and symptoms
 - Flushing
 - Osteoporosis or sclerosis
 - Lymph node involvement
 - Hepatomegaly, splenomegaly, may have increased bleeding with heparin
 - Pancytopenia
 - Heart, kidneys, GI tract, or lung may be affected
 - Mast cell leukemia (rare) portends poor prognosis
 - Other leukemias or lymphomas may develop
- Diagnosis (of cutaneous mastocytosis)/etiology
 - Histology
 - Accumulation of mast cells in skin
 - Dense dermal aggregate of mast cells
 - Mast cells stains: Leder, toluidine blue, Giemsa
 - Mutation of *c-kit* protooncogene receptor that codes for transmembrane tyrosine kinase (also in piebaldism)
 - Serum tryptase: useful screening test for systemic mastocytosis

QUIZ

Questions

1. An 18-month-old boy presents with large, progressively extending, blue-gray patches over his anterior and posterior trunk. What diagnosis should be considered?
 - A. Nevus of Ota
 - B. Nevus of Ito
 - C. Mosaic hypopigmentation
 - D. Neurofibromatosis
 - E. Lysosomal storage disease
2. A newborn is found to have multiple, dark blue, non-blanching papules in a generalized distribution. Each of the following diagnoses could be causative, EXCEPT:

- A. CMV infection
 - B. Rubella
 - C. Hemolytic disease of the newborn
 - D. Tuberous sclerosis
 - E. Hereditary spherocytosis
3. Which of the following features distinguish Finkelstein's disease from Henoch-Schonlein purpura?
 - A. Purpuric skin lesions that are targetoid or "cockade"
 - B. Edema of the face and distal extremities
 - C. Rapid resolution within 1–3 weeks
 - D. Rare renal, joint or gastrointestinal involvement
 - E. All of the above
 4. Histologic examination of a nevus anemicus shows:
 - A. Presence of melanocytes around blood vessels
 - B. Absence of melanocytes
 - C. Smooth muscle hamartoma
 - D. Collections of mast cells
 - E. Normal skin
 5. A 6-month-old infant is diagnosed with scabies. The treatment of choice is:
 - A. 10% sulfur in petrolatum
 - B. Topical 5% permethrin
 - C. Topical 1% permethrin
 - D. Oral ivermectin
 - E. Topical lindane
 6. In staphylococcal scaled skin syndrome, the bacterial toxin that is produced cleaves:
 - A. Desmoglein 3
 - B. Desmoglein 1
 - C. Bullous pemphigoid antigen 180
 - D. Alpha-6 beta-4 integrin
 - E. Plectin
 7. In the United States, Gianotti-Crosti syndrome is most commonly due to:
 - A. Hepatitis B virus
 - B. Group A *Streptococcus*
 - C. Cytomegalovirus (CMV)
 - D. Epstein-Barr virus (EBV)
 - E. Varicella-zoster virus
 8. A 2-day-old, otherwise healthy newborn presents with multiple erythematous papules and pustules. Microscopic examination of the contents of a pustule shows numerous eosinophils. The most likely diagnosis is:
 - A. Transient neonatal pustular melanosis
 - B. Erythema toxicum neonatorum
 - C. Acropustulosis of infancy
 - D. Impetigo
 - E. Contact dermatitis
 9. An 18-month-old girl with a history of constipation presents with a 3-month history of a triangular-shaped, soft, flesh-colored nodule on her perineal median raphe. The most likely diagnosis is:
 - A. Verruca
 - B. Histiocytosis
 - C. Perianal pyramidal protrusion
 - D. Lichen sclerosus et atrophicus
 - E. Pseudoverrucous papules and nodules
 10. A 4-year-old male presents with a linear clustering of verrucous, brown papules on his posterior leg that have been present since birth. The most likely diagnosis is:
 - A. Nevus sebaceous of Jadassohn
 - B. Lichen striatus
 - C. Linear epidermal nevus
 - D. Flat warts
 - E. Incontinentia pigmenti

Answers

1. E. Extensive Mongolian spots (dermal melanocytosis) with dorsal/ventral distribution, indistinct borders, and persistent and/or "progressive" behavior may be a sign of underlying lysosomal storage disease (most commonly GM1 gangliosidosis type 1 and Hurler disease).
2. D. Multiple, dark blue to magenta, small, non-blanching papules and macules, present at birth or by the first day of life, are a sign of extramedullary hematopoiesis. This is associated with congenital infections (TORCH viruses, most commonly cytomegalovirus), hemolytic disease of the newborn, hereditary spherocytosis, and twin-twin transfusion syndrome. It is NOT associated with tuberous sclerosis.
3. E. Finkelstein's disease is an acute form of leukocytoclastic vasculitis. It affects children under 2 years of age, has a rapid onset; often follows a preceding infection, and is accompanied by fever, edema, and targetoid purpuric lesions on the face, ears, and distal extremities. Children generally appear well despite alarming appearance of skin lesions. Renal, joint, and GI involvement is exceptional (important difference from adult Henoch-Schonlein purpura).
4. E. Histologic examination of a nevus anemicus shows normal skin.

5. B. Topical 5% permethrin is the treatment of choice (approved down to 2 months of age). For newborn infants or pregnant/nursing women, 6% to 10% sulfur in petrolatum is the recommended treatment (permethrin is pregnancy category factor B).
6. B. Staphylococcal scalded skin syndrome occurs due to the epidermolytic toxin of *Staphylococcus* phage group II which cleaves desmoglein 1.
7. D. Gianotti-Crosti syndrome is associated with viral infections: Epstein-Barr virus (most common association in the United States), hepatitis B virus, cytomegalovirus (CMV), and respiratory syncytial virus (RSV)
8. B. Erythema toxicum is a common newborn rash, affecting half of full-term newborns. It appears as a "flea-bitten rash" of few to hundreds of erythematous macules, wheals, papules, and pustules. Microscopic examination of the contents of a pustule will show numerous eosinophils. It occurs in the first 24 to 48 hours of life and resolves during the first 1–2 weeks of life.
9. C. Perianal pyramidal protrusion is a triangular-shaped, flesh-colored to erythematous nodule on the perineal median raphe, anterior to the anus. More than 90% of cases occur in female infants. The average age at presentation is 14 months. It is related to constipation and possibly lichen

sclerosus et atrophicus. Perianal pyramidal protrusion resolves spontaneously over several months to 1 to 2 years. Treating the associated constipation may hasten resolution.

10. C. Linear epidermal nevus contains verrucous pink to brown papules following Blaschko's lines. It is generally present at birth or within first year of life, but sometimes later in childhood or adolescence.

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CUTANEOUS INFESTATIONS

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PARASITE

- An organism that lives on or within another organism (host)
- A parasite causes harm to the host. This distinguishes parasitism from commensalism, in which the host derives no benefit but is not injured, and mutualism, where the relationship benefits both organisms
- Host, in addition to providing a steady food source, provides warmth and shelter
- Definitive host: parasite becomes sexually mature and undergoes reproduction
- Reservoir hosts are those in which parasites that are pathogenic to other animals or to humans
- Vector: agent by which a parasite is transmitted to the host (e.g., arthropod, mollusk)

ARTHROPODA

- Bites usually result in localized, cutaneous reactions and pruritus
- Some of these organisms are medically important: Fleas, lice, and ticks can transmit lethal epidemic disorders
- Many of these vector-transmitted diseases are endemic in various regions of the world
- Four classes of arthropods are of dermatologic interest and are covered in this chapter:
 - Chilopoda: including centipedes
 - Diplopoda: including millipedes
 - Insecta: including caterpillars, moths, bedbugs, lice, flies, mosquitoes, beetles, bees, wasps, hornets, fire ants, and fleas
 - Arachnida: including ticks, mites, scorpions, and spiders

- Organisms from the arthropod classes Arachnida and Insecta have a hard-jointed exoskeleton and paired, jointed legs
- Class Insecta: a group of organisms with six legs and three body segments: head, thorax, and abdomen. Includes the following orders
 - Siphonaptera: fleas
 - Anoplura: head and body lice
 - Pthiridae: crab louse
 - Diptera: two-winged flies, mosquitos, midges
 - Hemiptera: true bugs
 - Lepidoptera: butterflies, moths, and their caterpillars
 - Hymenoptera: ants, wasps and bees
- Class Arachnida: a group of organisms with eight legs and two body segments: cephalothorax and abdomen
 - Ixodidae: hard ticks
 - Argasidae: soft ticks
 - Araneae: spiders
- Centipedes and millipedes

INSECTA

Siphonaptera (Fleas)

- Wingless, laterally compressed insects with a hard, shiny integument
- The body has three regions: head, thorax, and abdomen
- Mouthparts are modified (paired maxillary palpi) for piercing and sucking
- Survive months without feeding
- Order *Siphonaptera* contains two flea families of medical importance
 - *Pulicidae*: (human, cat, dog, and bird fleas)
 - *Sarcopsyllidae* (also called *Tungidae*): the sand flea
- Fleas jump, on average, about 20 cm

- One flea can bite two to three times over a small area
 - Bites produce irregular, pruritic, red wheals up to 1 cm in diameter
 - Patients may present with a surrounding halo with a central papule, vesicle, or bulla or with hemorrhagic macules, papules, vesicles, or bullae
1. *Pulex irritans* (human flea) (Fig. 16-1)
 - Farms, urban areas, predominant flea on dogs in portions of the Carolinas
 2. *Tunga penetrans* (chigoe flea)
 - Tropical and subtropical regions of North and South America, Africa
 - Intense itching and local inflammation
 - Causes tungiasis
 - Female sand flea, which burrows into human skin at the point of contact, usually the feet
 - Head is down into the upper dermis feeding from blood vessels
 - Caudal tip of the abdomen is at the skin surface
 - Nodule (usually on the foot) that slowly enlarges over a few weeks
 - Treatment
 - Occlusive petrolatum suffocates the organism.
 - Lindane, dimethyl phthalate, or dimethyl carbamate
 3. *Xenopsylla cheopis* (Oriental rat flea)
 - Plague (*Yersinia pestis*)
 - Endemic (murine) typhus (*Rickettsia typhi*)
 4. Cat flea (*Ctenocephalides felis*)
 - Endemic (murine) typhus (*Rickettsia felis*)

Anoplura

PEDICULIDAE

- After attaching to the skin, these flattened, wingless insects feed on human blood and can cause intense itching



FIGURE 16-1 *Pulex irritans* (human flea).

- They will die of starvation if kept off the body for more than 10 days
 - They are also killed by washing in water at 53.5°C for 5 minutes
 - Life span of a louse is about 30 to 45 days
1. *Pediculus humanus corporis* (body louse)
 - Up to 5 mm long
 - Vector for
 - Epidemic typhus (*Rickettsia prowazekii*)
 - Trench fever, bacillary angiomatosis, bacillary peliosis (*Bartonella quintana*)
 - Relapsing fever (*Borrelia recurrentis*, *Borrelia duttoni*)
 - Crowded, unsanitary conditions
 - Lives in clothing and moves to body to feed
 - Pyoderma involving areas covered by clothing, most notably the trunk, axillae, and groin; erythematous macules, papules, and wheals, as well as excoriations, also may be seen
 - Treatment: malathion 1% powder, permethrin spray
 2. *Pediculus humanus capitus* (head louse) (Fig. 16-2)
 - Whitish in color and up to 3 mm long
 - Confined to the scalp
 - Lice and their eggs can withstand vigorous washing and combing
 - Nits: cementing of white eggs to the hair; usually found in the warm areas of the scalp such as behind the ears and on the posterior neck
 - Eggs hatch in approximately 7 to 9 days
 - Treatment: requires that both the adult lice and the nits be killed



FIGURE 16-2 *Pediculus humanus capitus* (head louse).

- Two treatments one week apart are recommended because nits hatch in 7 days
- Occlusive agents that kill via asphyxiation
- Malathion lotion
- Natural pyrethrin products and synthetic pyrethroids
- Lindane, gamma-benzene hexachloride
- Nits are best removed with a comb after soaking the hair in a vinegar or formic acid solution to flatten the cuticle and facilitate combing.

Pthiridae

- *Pthirus pubis* (Fig. 16-3)
 - Pubic louse, crab louse
 - Short, broad body with rather stout claws on the middle and hind legs
 - Reddish brown in color
 - Often sexually transmitted
 - Rarely involves facial (eyelashes), chest, or axillary hair
 - Patients can remain asymptomatic for up to a month before pruritus develops; nits, similar to those in pediculosis capitis, are seen
 - Blue macules (maculae ceruleae) are often seen on the surrounding skin and are believed to be produced by louse saliva acting on blood products
 - Treatment: lotions or shampoos containing 1% lindane, 0.3% pyrethrins, or 5% permethrin, asphyxiating agents
 - Infestation of the eyelashes: petrolatum or fluoroscein

Diptera

- Two-winged, biting insects

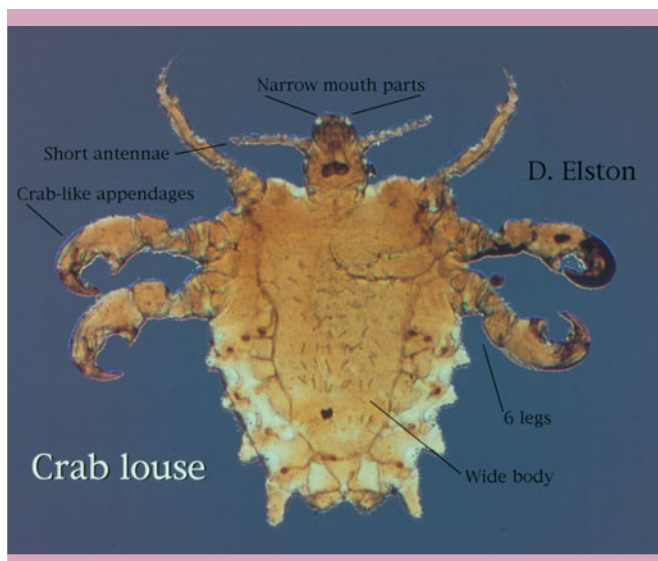


FIGURE 16-3 *Pthirus pubis* (pubic or crab louse). (Courtesy of Dr. Dirk M. Elston)

- All require a blood meal at some time in their development
- Bites can manifest as immediate urticarial papules, delayed erythematous papules, or both

FLIES

- Number of infectious diseases can be transmitted by biting flies
- A variety of flies commonly bite humans
- Common housefly does not bite but rather feeds on the surface of the skin
- Wound myiasis: eggs are deposited on an open wound
- Furuncular myiasis: solitary furuncle-like lesions often transferred by a mosquito vector
- Plaque myiasis: grouped boil-like lesions caused by eggs laid on wet laundry

DERMATOBIA HOMINIS (BOTFLY)

- Most common cause of furuncular myiasis
- Occurs when fly larvae (maggots) invade tissue
- Raised, erythematous papule develops at the site of the bite, most frequently on the distal extremity or scalp
- Enlarges to become an indurated nodule with a central punctum, which is the breathing hole for the larva
- Treatment
 - Surgical excision; occlusion

SAND FLIES (*PHLEBOTOMUS* AND *LUTZOMYIA*)

- Vectors for bartonellosis (*Bartonella bacilliformis*-Oroya fever, Carrion's disease) and leishmaniasis
- Leishmaniasis
- *Leishmania*: protozoan infection
- *Leishmania* transform to the *promastigote* (or flagellate) form in the gut of the vector
 - Promastigote is a slender organism with a flagellum
 - After replicating, the promastigotes migrate to the sandfly's proboscis, from which they are regurgitated into the next host as the sandfly feeds
- Located within reticuloendothelial cells of infected tissues, *Leishmania* exist in an amastigote (nonflagellate) form
- Vector: sand fly (*Phlebotomus* and *Lutzomyia* species)
- Clinical
 - Cutaneous
 - Nontender, firm, red papule at bite
 - Lesion widens with central ulceration, serous crusting, and granulomas
 - Lesions may be wet or dry and become fibrotic or hyperkeratotic with healing

- Mucocutaneous
 - Excessive tissue obstructing the nares, septal granulation, and perforation
 - Gingivitis, periodontitis, and localized lymphadenopathy
- Visceral (kala-azar/black fever)
 - Systemic infection of the liver, spleen, and bone marrow
 - *L. donovani* and *L. infantum*
 - Recurrent high fevers, wasting, anorexia, night sweats, diarrhea, and malaise
- *Leishmaniasis recidivans*
 - Occur years after a localized cutaneous lesion has healed
 - New ulcers and papules form over the edge of the old scar
- After kala-azar
 - Multiple, hypopigmented, erythematous macules
- Old World
 - *L. tropica* and *L. major*
 - Southwest Asia, Indian subcontinent, Mediterranean, East Africa, and republics of the former Soviet Union
 - Visceral leishmaniasis
 - Diffuse cutaneous leishmaniasis
 - *L. aethiopica*
- New World
 - Throughout the Americas
 - Visceral disease
 - *L. chagasi*
 - Cutaneous lesions
 - *L. mexicana*
 - Solitary nodule
 - Mucocutaneous disease (espundia)
 - *L. braziliensis*
 - *Leishmaniasis recidivans*
 - *L. viannia braziliensis*
 - Diffuse cutaneous leishmaniasis
 - *L. mexicana*
 - *L. amazonensis*
 - Post-kala-azar leishmaniasis
 - *L. donovani chagasi*
- Diagnosis
 - Culture
 - Direct agglutination test, immunofluorescence assay, or enzyme-linked immunosorbent assay (ELISA)
 - Montenegro skin test: determines delayed-type hypersensitivity reactions
- Treatment
 - Pentavalent antimony, administered intravenously or intramuscularly
 - Amphotericin B and pentamidine

TSETSE FLY (GLOSSINA), GLOSSINIDAE FAMILY

- Vector for African trypanosomiasis (sleeping sickness)

- Trypanosomes are ingested during a blood meal by the tsetse fly from a human reservoir, develop into epimastigotes, and are reinfected into human hosts
- Extensive antigenic variation of parasite surface glycoproteins
- West African (*T. brucei gambiense*)
 - Slow progression
- East African (*T. brucei rhodesiense*)
 - Rapid progression (within a week)
- Stage 1
 - Chancre
 - Hypersensitivity reaction: urticaria, pruritus, facial edema, fever, arthralgias, Winterbottom's sign (posterior cervical lymphadenopathy)
 - Kerandel's sign: delayed sensation to pain or a sensation of hyperesthesia
- Stage 2: central nervous system (CNS) changes
 - Headaches, behavioral changes, seizures in children
- Laboratory studies
 - Anemia, hypergammaglobulinemia, elevated erythrocyte sedimentation rate (ESR), thrombocytopenia, and hypoalbuminemia
 - Wet smear of unstained blood, bone marrow, spinal fluid, skin lesions: parasite is visualized
 - Card agglutination test for trypanosomiasis (CATT)
- Treatment
 - Early stages: suramin, pentamidine
 - CNS stage: intravenous melarsoprol B, eflornithine

CHRYSOPS (DEER FLY)

- Vector for loaisis (see below)

MOSQUITOES

- Belong to the family *Culicidae*
- Delicate winged insects with long proboscises and long, thin legs
- Require water to mature through the larval and pupal stages
- Can be the vector for filariasis, yellow fever, dengue fever, encephalitis and malaria
- Cutaneous reactions to bites include urticarial wheals, delayed papules, bullous lesions, hemorrhagic necrotic lesions, excoriations, eczematous patches, and granulomatous nodules

CULEX

- Vector for
 - Japanese encephalitis
 - Murray Valley encephalitis virus
 - Rift Valley fever
 - Ross River virus
 - *Sindbis* virus

- St. Louis encephalitis (*Flaviviridae*)
- West Nile fever: arthropathy, muscle weakness, rash
- Filariasis (*Wuchereria bancrofti*)
- Dirofilariasis: *Dirofilaria immitis* (dog heart worm), *Dirofilaria tenuis* (raccoons), *Dirofilaria repens* (dogs), *Dirofilaria ursi* (bears)

ANOPHELES

- Vector for malaria (*Plasmodium falciparum*, *P. malariae*, *P. vivax*, *P. ovale*)

Aedes Aegypti

- Yellow fever (*Flaviviridae*)
- Dengue

BEETLES

- Blister beetles cause cutaneous injury when a potent vesicating agent, cantharidin, is released from their bodies and contacts human skin
- *Lytta vesicatoria*, also known as “Spanish fly,” is the source of cantharidin
- Two species, *Epicauta vittata* (striped blister beetle) and *E. pennsylvanica* (black blister beetle), are widely distributed in the United States, although more than 100 other species occur in various parts of the United States
- Blisters develop within a day and then dry up and desquamate in about a week
- Treatment: affected skin should be washed immediately with alcohol or acetone to dissolve or dilute the cantharidin

Hemiptera (True Bugs)

CIMEX LECTULARIUS (BED BUG)

- Feeds nocturnally on human blood
- 8 mm long, reddish brown, and wingless, with a greatly flattened body
- Linear arrangement of large wheals, often > 1 cm, which are accompanied by itching and inflammation
- Bullous eruptions can occur
- Transmission of trypanosomiasis and possibly hepatitis

REDUVID BUG (KISSING BUG, ASSASSIN BUG)

- Vector for Chagas’ disease (American trypanosomiasis) caused by *T. cruzi*
- 15 mm long, dark brown in color
- *Reduviid* bug ingests the trypomastigote while feeding on infected animals; it then divides and transforms in the gut of the bug into metacyclic trypomastigotes
- Bug ventures out at night to feed on exposed skin; deposit stool when biting; 80% enter through conjunctiva

- Transform into amastigotes after ingestion by macrophages; *T. cruzi* burst from the macrophages as trypomastigotes and disseminate widely to invade most human tissues
- Lymphatic spread then carries the organism to regional lymph nodes
- Chagoma: red nodule at site of bite; lasts only a few days to a couple of weeks
- Ramaña’s sign: bite near the eye causes unilateral periorbital conjunctivitis and edema
- Hematogenous dissemination: acute phase with fever to 104°F, vomiting, diarrhea, cough, hepatosplenomegaly, edema, myocarditis, seizures, and meningoencephalitis
- Latent phase: myocardial heart disease, with fibrosis, conduction defects
- Cardiac involvement: congestive heart failure
- Gastrointestinal system affected: dysphagia and abdominal pain, constipation secondary to megacolon (owing to destruction of the parasympathetic ganglion)
- Sequelae of myocardial damage, megacolon, megaesophagus
- Diagnosis: parasites are relatively numerous initially and easily demonstrable on peripheral blood smear
- Treatment: benzimidazole, nifurtimox

Lepidoptera (Caterpillars)

1. *Automeris io* (family Saturniidae)
 - Io moth
 - East of the Rocky Mountains from Canada to Mexico
 - Feed on deciduous (broadleaf) trees and herbaceous plants
 - Yellow-green with red and white lateral stripes
 - Urticating spines
2. *Megalopyge opercularis* (puss caterpillar, asp caterpillar) (Fig. 16-4)
 - Broad and flat
 - Dense covering of long, silky, gray to reddish brown hairs
 - Urticating spines dispersed among the hairs
3. *Sibine stimulea* (saddleback caterpillar)
 - Brown at both ends
 - Green around the middle “saddle blanket”
 - Purple-brown oval-spot “saddle”
 - Urticating spines along the sides and at the front and rear of the body
4. Hagmoth: brown with nine pairs of variable-length lateral processes with urticating hairs
5. Buck moth
 - Purple-black with a reddish head
 - Pale-yellow dots scattered over the body with reddish to black branches
 - Stinging spines arising from tubercles

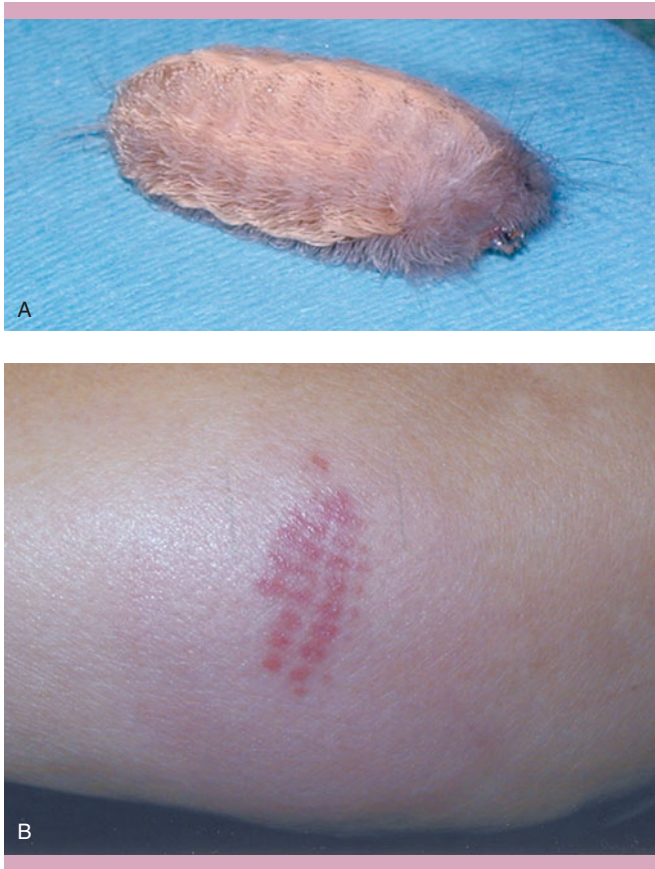


FIGURE 16-4 *Megalopyge opeucularis* (puss caterpillar, asp caterpillar). (From Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003, p. 2297.)

Hymenoptera

- Known for producing a painful sting that rarely may result in anaphylaxis and death
- Reactions produced by *Hymenoptera* stings
- Local: erythema, edema, and pain at the site of the sting
- Wells' syndrome, consisting of erythematous, edematous plaques composed histologically of eosinophilic granulomatous dermatitis
- Systemic toxic venom
- From multiple stings
- Constitutional symptoms
- Systemic allergic
- Immunoglobulin (Ig) E antibodies cause degranulation and the release of vasoactive substances: urticaria and angioedema
- Other: serum sickness, acute renal failure, possible Guillain-Barré syndrome

SUBORDER: APOCRITA—ANTS, WASPS AND BEES

1. Formicidae: ants

- *Solenopsis* (fire ant)
 - Alkaloid venom contains phospholipase and hyaluronidase
 - May be red or black and live in ground colonies
 - Sting by first biting the victim with their powerful set of pincer jaws and then swiveling and stinging in a circular pattern
 - Pustules, burning itch
- 2. *Vespidae*: yellowjackets, hornets, paper wasps
 - Paper wasps build hives under the eaves of buildings
 - Yellow jackets are ground-nesting
 - Hornets reside in shrubs and trees
- 3. *Apoidea* family
 - Bumble bees and honey bees
 - Honeybees feed on flowering plants
 - Stinger contains a barb, causing it to be left on the victim along with the venom sac
 - This act eviscerates and kills the bee

ARACHNIDA

- Adult forms have four pairs of legs, six-legged larvae common among ticks and mites; may cause human injury by biting, burrowing in, and feeding on skin, stinging, and delivering toxic venom
- Ticks
 - Tick-bite alopecia
 - Patchy alopecia at the site of tick attachment
 - Hair loss begins about 1 week after the tick is removed
 - Tick paralysis
 - *Dermacentor* ticks in North America
 - *Ixodes* ticks in Australia
 - Ascending flaccid paralysis
 - Symptoms usually disappear rapidly if the tick is found and removed
 - Tick-bite pyrexia
 - While the tick feeds, the host may develop fever, chills, headache, abdominal pain, and vomiting
- Natural parasites of many different animals, including mammals, birds, reptiles, and amphibians
- Vectors for numerous infectious diseases
- Two families of ticks:
 - Hard ticks (*Ixodidae*)
 - Hard chitinous dorsal shield
 - Can endure cold, humid weather
 - Soft ticks (*Argasidae*)
 - Lack a dorsal shield
 - Prefer drier environments where they live in close association with an animal host

- Most ticks fast for long periods because they cannot live on vegetable matter; blood meal is acquired mostly by chance
- Feeding is usually complete within 6 to 7 days, but the tick can remain attached to the host for an unspecified period
- Ticks require a blood meal before they can lay eggs
- Body of mites and ticks
 - Divided into two regions
 - Anterior: cephalothorax (or prosoma)
 - Posterior: abdomen (or opisthosoma)

Mites

CHEYLETIELLA

- “Walking dandruff”: caused by movement of mite under scales
- Live on keratin layer of small mammals (dogs, cats, rabbits)
- Pruritic dermatitis in humans who handle pets

Liponyssoides (Formerly *Allodermanyssus*) *sanguineus*

- House mouse mite
- Rickettsial pox (*Rickettsia akari*)

Ornithonyssus sylviarum

- Found in birds and domestic fowl
- Bird handlers are bitten most commonly

Dermanyssus gallinae and *Ornithonyssus bursa*

- Can infest domestic poultry

Dermatophagoides (Family *Pyroglyphidae*)

- House dust mite
- Tiny, translucent mites, generally less than 0.2 mm long
- Cause severe asthma and other allergic complaints in humans
- Humidity levels below 60% appear to support fewer mites

Family *Demodicidae*

DEMODEX FOLLICULORUM (FIG. 16-5)

- Elongate, microscopic mites
- Live in hair follicles and sebaceous glands
- Generally asymptomatic
- May cause folliculitis
- Associated with rosacea

Harvest Mites (Family *Trombididae*)

TROMBICULIDAE (CHIGGER, “RED MITE”)

- Only the six-legged larval form parasitizes other animals
- Attach to a host, feed for 2 to 3 days, molt to the nymphal stage, and then leave the host

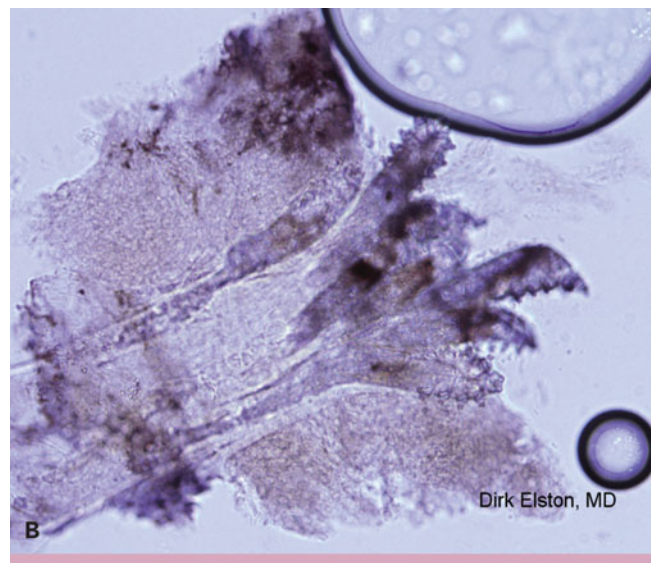
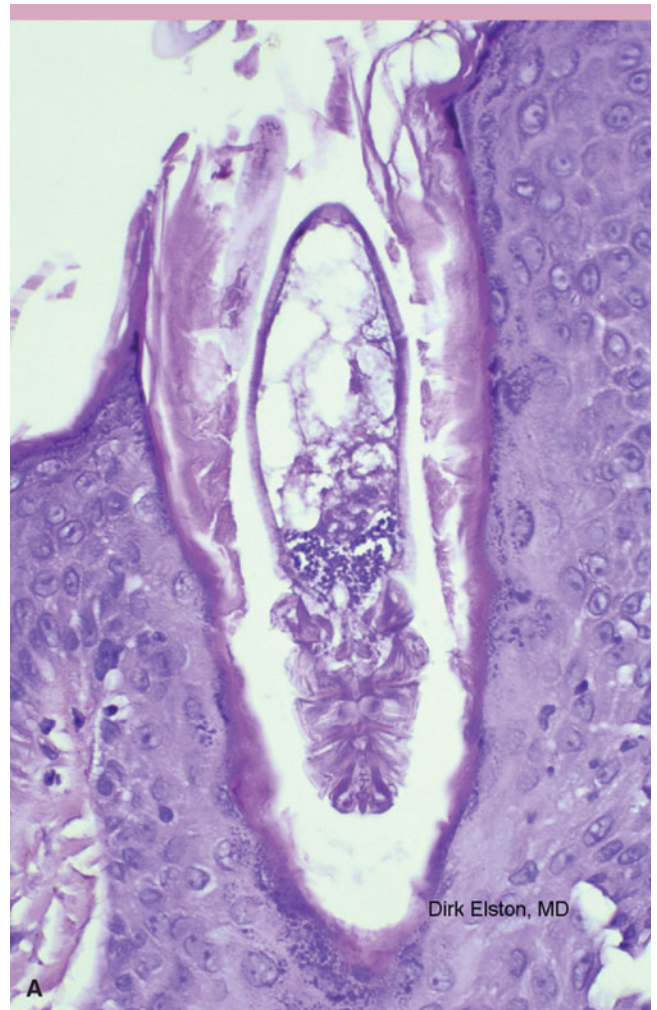


FIGURE 16-5 *Demodex folliculorum*. (Courtesy of Dr. Dirk Elston.)

- Skin lesions develop 3 to 24 hours later when an allergic reaction to mite saliva develops
- Pruritic red papules grouped about the waist, thighs, and legs
- Can persist for several weeks
- *Eutrombicula alfreddugesi* most common variety in the United States
- *Neotrombicula autumnalis* most common variety in Europe
- Scrub typhus (*Rickettsia tsutsugamushi*)

Scabies or Itch Mites (Family Sarcoptidae)

SARCOPTES SCABEI (FIG. 16-6)

- Globular, semitranslucent mites, less than 0.3 mm long
- Adult mites copulate on the skin, after which the female will burrow, laying her eggs along the way
- Six-legged larvae hatch and take 10 to 14 days before becoming adults
- They survive off the human body for only 2 to 3 days
- Symptoms take 30 days after an immune response develops to the mites or their excrement (scybala)
- Spread by close personal contact
- Hands and wrists are affected most often
- Burrows, which are produced by the adult female mite, and erythematous papules
- In adult patients, the scalp and face are uninvolved
- Pruritus of scabies generally is severe and most noticeable at night
- Diagnosis: mites, eggs, larvae, or scybala on microscopic examination of lesional skin scrapings
- Nodular scabies
 - Erythematous, firm nodules that persist for weeks to months after treatment
- Norwegian scabies
 - Seen in immunocompromised or debilitated patients
- Thick, scaling, crusted plaques that are found most commonly on the hands, feet, and scalp but may be generalized in distribution
- Lesions contain thousands of mites
- Treatment
 - 5% permethrin
 - Lindane: avoid in young children and pregnant women owing to reports of neurotoxicity
 - 5% to 10% precipitated sulfur in petrolatum
 - 25% crotamiton
 - oral ivermectin
 - Nodular scabies: topical or intralesional injection of a corticosteroid

Hard or Shield Ticks (Family Ixodidae)

- Wingless arthropods
- Eight-legged as adults, six-legged larva
- Flattened dorsoventrally
- Often teardrop-shaped from dorsal view
- Scutum (shield) on the dorsal surface
- 1. *Ixodes* tick
 - *I. scapularis*: eastern United States
 - *I. pacificus*: in California
 - *I. ricinus*: in Europe
 - Vector for
 - Lyme disease (*Borrelia burgdorferi*)
 - Babesiosis
 - Anaplasmosis
- 2. *Amblyoma americanum* (lone star tick) (Fig. 16-7)
 - Prominent white dot on the back of the adult female
 - Primarily found in the southern United States, although the range is expanding
 - Vector for
 - Rocky Mountain spotted fever (*Rickettsia rickettsii*)
 - Ehrlichiosis (*Ehrlichia chaffeensis*)

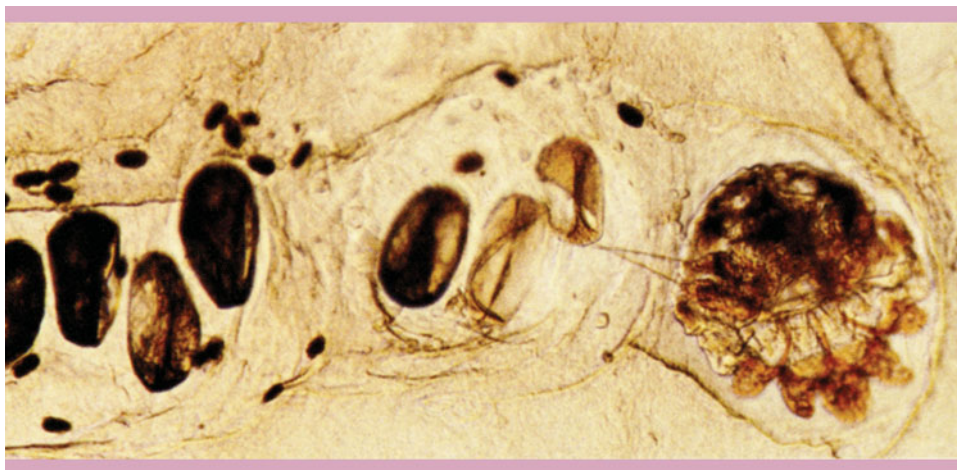


FIGURE 16-6 *Sarcoptes scabiei*. (Reprinted with permission from Wolff and Johnson: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 6th Ed. New York: McGraw-Hill; 2009.)

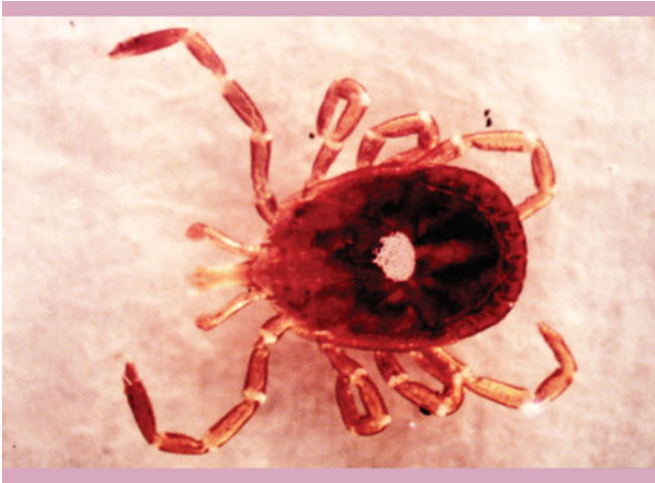


FIGURE 16-7 *Amblyoma americanum* (lone star tick). (Reprinted with permission from Knoop et al. *Atlas of Emergency Medicine*, 2nd Ed. New York: McGraw-Hill; 2002.)

- Tularemia (*Francisella tularensis*)
- *Amblyomma maculatum* (Gulf Coast tick): tick paralysis
- 3. *Dermacentor* (Fig. 16-8)
 - Rocky Mountain spotted fever
 - Ehrlichiosis
 - Tularemia
 - Colorado tick fever
 - Causative agent, an RNA virus of the genus *Orbivirus* of the family Reoviridae
 - Limited to *D. andersoni*
 - *D. andersoni*
 - Wood tick
 - Western United States



FIGURE 16-8 *Dermacentor*. (Reprinted with permission from Knoop et al. *Atlas of Emergency Medicine*, 2nd Ed. New York: McGraw-Hill; 2002.)

- Adults are generally brown but become slate gray when engorged
- Commonly involved with tick paralysis
- Female: dark reddish brown with a white shield covering the front third of the body
- Male: grayish-white shield area on top of the body
- Tick paralysis
- *D. variabilis*
 - Dog tick
 - Eastern United States
 - Tick paralysis

Soft or Leathery Ticks (Family Argasidae)

- *Ornithodoros hermsi*, *O. parkeri*, *O. turicata*
- Light gray and leathery in appearance
- Mouthparts are hidden underneath the body
- Transmits relapsing fever: *Borrelia duttoni*, *B. recurrentis*

Araneae (Spiders)

- All spiders have a cephalothorax from which extend eight legs and an abdomen
- A pair of jaws (chelicerae) are found at the anterior end of the cephalothorax
- Jaws terminate in sharp, chitinized fangs from which venom is ejected

Lactrodectus mactans (Black Widow) (Fig. 16-9)

- Eastern and central regions of the United States
- Black with a globose abdomen that has the characteristic red hourglass-like marking on the ventral surface



FIGURE 16-9 *Lactrodectus mactans* (black widow spider). (Reprinted with permission from Wolff et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- Prefer a warm, dry environment and can be found both outdoors and inside buildings
- Only the female of the species is capable of envenomating humans
- Neurotoxin (α -latrotoxin): causes release of acetylcholine and catecholamines at neuromuscular junction
- Ca^{2+} -dependent release of neurotransmitters down the concentration gradient ensues: no reuptake of the neurotransmitters
- Bite: two tiny red puncta; urticarial with white halo, local piloerection; little local damage
- Systemic symptoms begin within an hour, peak at 1 to 6 hours, and can last 1 to 2 days
- Severe myalgias and muscle cramping regionally and then throughout the body
- Abdominal musculature is involved and may simulate an acute surgical abdomen
- Painful lymphadenopathy, hypertension, profuse sweating, nausea, and tremors
- Treatment: symptomatic—narcotics, muscle relaxants, and intravenous calcium gluconate
- Spider antivenin

Loxosceles Recluse (Brown Recluse) (Fig. 16-10)

- Violin-like marking on dorsal aspect of the cephalothorax
- Yellow to brown cephalothorax and a tan abdomen
- From 1 to 1.5 cm in length
- South central part of the United States; they avoid daylight
- Necrotic arachnidism and disseminated intravascular coagulation



FIGURE 16-10 *Loxosceles reclusa* (brown recluse spider).

- Phospholipase (sphingomyelinase D) causes platelet aggregation, thrombosis, and massive neutrophil infiltration
- Initial bite is often painless and unnoticed by the patient; central papule and associated erythema
- Flag sign
 - Central blue-gray area due to thrombosis
 - Blanched halo from arterial spasm
 - A large surrounding area of reactive erythema
- Progression to eschar formation, dermal necrosis, and stellate ulceration
- Systemic: hematuria, anemia, constitutional symptoms, rash, cyanosis, and severe intravascular hemolysis
- Treatment
 - Tetanus toxoid
 - Rest, ice and elevation
 - Antibiotics if superficial infection develops
 - Data are mixed concerning triamcinolone and dapsone. A delay of even 1 hour may negate any effect of dapsone

Scorpions

- Large arachnids with an elongated abdomen that terminates in a stinger
- Abdominal glands that release both neurotoxic and hemolytic venom into the stinger
- Nocturnal and hide during the daytime in dark places
- Pain and swelling at the site of sting
- Neurotoxin can result in: localized numbness, fasciculation, lacrimation, salivation, profuse sweating, urinary urgency, nausea, tongue paresthesia, restlessness, convulsions, and an increase in extraocular muscle activity
- *Centruroides sculpturatus* most toxic in United States, although it rarely results in death
- Highly dangerous scorpions include *Parabuthus*, *Uroplectes* and *Tityus* species
- Treatment
 - Remove the stinger
 - Cool the site with ice; antivenin
 - Barbiturates or diazepam for the central nervous system hyperactivity
 - Atropine for cholinergic side effects of the neurotoxin

CENTIPEDES AND MILLIPEDES

American Centipedes

- Slender, segmented body that ranges in color from yellow to green to brown or black and may vary in length from 1 to 30 cm

- Nocturnal carnivores and prefer a dark, moist environment like that found under rocks and logs
- *Scutigera* species
 - Found in the eastern United States
 - Does not sting humans
- *Scolopendra* species
 - Western United States and Hawaii
 - Can inflict a painful sting
 - Immediate reaction consists of local burning pain
 - Chevron-shaped bite
 - Occasionally, local necrosis, regional lymphangitis, and lymphadenopathy
- Treatment
 - Cleanse the wound
 - Inject a local anesthetic into the wound
 - Tetanus prophylaxis
 - Systemic antihistamines

Millipedes

- Multisegmented, with a hard, often brightly colored exoskeleton
- Nocturnal vegetarians that prefer dark, moist environments
- When disturbed, some millipedes will coil into a tight spiral and then secrete a toxic liquid from repugnatorial glands located on the sides of each segment
- Causes an immediate burning sensation when it contacts human skin
- Skin then becomes yellow-brown and in 24 hours develops intense erythema and often vesiculation
- Treatment: immediate lavage of the area with alcohol or water

PROTOZOA

Cutaneous Amebiasis

- *Entamoeba histolytica*
- Humans are the major reservoir
- Clinical presentation includes an acute dysenteric form and a less symptomatic nondysenteric intestinal form
- Life cycle: cysts travel to the small intestine after ingestion from fecally contaminated food or water
- Trophozoites are released
- They reencyst and produce asymptomatic infection (resolves spontaneously within 12 months) or parasite causes symptomatic amebiasis
- Intestinal disease: acute proctocolitis (dysentery)
- Extraintestinal disease: brain and liver amebic abscesses, peritonitis, pericarditis, cutaneous lesions of amebiasis seem to be extremely rare (direct extension of intestinal disease); with painful ulcerations that may enlarge rapidly

- Diagnosis: indirect hemagglutination, immunofluorescence, and ELISAs
- Treatment: metronidazole, iodoquinol, paromomycin

HELMINTHIC INFECTIONS

- *Helminth* is derived from the Greek word *helmins*, meaning “worm”
- Categorized as
 - Annelids (i.e., phylum Annelida, the segmented worms)
 - Nematodes (i.e., phylum Nematoda, the roundworms)
 - Platyhelminths (i.e., phylum Platyhelminthes, the flatworms)
 - Trematodes (i.e., flukes) and cestodes (i.e., tapeworms)

SOIL-MEDIATED HELMINTHIC INFECTIONS

NEMATODES (ROUNDWORMS)

- Hookworm: *Ancylostoma* and *Necator*
- Strongyloidiasis
- Ascariasis
- Enterobiasis
- Trichinosis
- Dracunculiasis
- Filariasis: loiasis, onchocerciasis
- Hookworms: caused by the roundworms

ANCYLOSTOMA DUODENALE, *NECATOR AMERICANUS*

- Ground itch
- Life cycle: female worms, residing in the host's small intestine, release eggs that are passed in the feces
- Larvae in the soil penetrate foot and migrate to lungs through the venous system
- Larvae are then coughed up and swallowed, and they end up in the intestine and mature into adults
- Pruritic, erythematous, edematous, linear, threadlike tracts marking larval migration in the skin
- Gastrointestinal bleeding, iron-deficiency anemia, hypoproteinemia
- Treatment: mebendazole, albendazole

CUTANEOUS LARVA MIGRANS (CREEPING ERUPTION) (FIG. 16-11)

- *Ancylostoma braziliensis*, hookworm of wild and domestic dogs and cats
- Most common cause of cutaneous larva migrans; human is a dead-end host



FIGURE 16-11 Cutaneous larva migrans (creeping eruption). (Reprinted from Wolff, Johnson, and Suurmond, *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 5th Ed, New York; McGraw-Hill; 2002.)

- Eggs are passed from animal feces into warm, moist, sandy soil, where the larvae hatch
- Larva penetrate skin directly but cannot penetrate basement membrane
- Larvae migrate slowly (2 cm/day) in skin, lack the ability to invade further, and complete their life cycle
- Produce raised, threadlike, serpiginous, pruritic, erythematous tracks
- Treatment: topical thiabendazole, ivermectin, albendazole

STRONGYLOIDES (LARVA CURRENS, "RACING LARVA")

- *Strongyloides stercoralis* (known as threadworm)
- Nematodes live in the small intestine
- Eggs hatch into larvae (rhabditiform), which are passed in the feces

- Larvae can penetrate skin of the host (quick migration rate of 5 to 10 cm/h) and then penetrate basement membrane to affect lungs and the gastrointestinal tract
- Larvae subsequently are swallowed and reach the small intestine
- Intense pruritus, purpura, serpentine urticarial streaks
- Autoinfection: transformation of noninfective larvae (rhabditiform) into infective larvae (filariform)
- Chronic strongyloidiasis
- Serpiginous wheals beginning perianally and extending to the buttocks, upper thighs, and abdomen
- Hemorrhagic pneumonia can result
- Stool for ova and parasites
- Enterotest (string test) or duodenal aspiration to examine duodenal fluid
- Blood cultures
- Enzyme immunoassay (EIA), indirect fluorescent antibody (IFA)
- Chest radiograph to reveal possible patchy alveolar infiltrate
- Sputum examination
- Loeffler's syndrome: eosinophilia, pneumonitis
- Treatment: thiabendazole, albendazole, ivermectin

ASCARIASIS

- *Ascaris lumbricoides*
- Adult worms live in the small intestine; eggs are laid and then passed out in the feces
- Eggs may remain viable in soil up to 17 months
- Larvae develop within the eggs
- Eggs are ingested or inhaled from soil; larvae hatch and move to heart, lungs, and pharynx
- Swallowed larvae mature into adults in intestine
- Urticaria
- Gastrointestinal symptoms/obstruction
- Cough, dyspnea, asthma, and chest pain
- Stool examination for ova and parasites
- Treatment: mebendazole, pyrantel pamoate

ENTEROBIASIS (PINWORM DISEASE)

- *Enterobius vermicularis*
- Most common helminth infection in industrialized countries
- After ingestion, eggs usually hatch in the duodenum within 6 hours
- Female worm migrates to the rectum after copulation and, if not expelled during defecation, migrates to the perineum (often at night)
- Pruritus ani, bruxism
- Diagnosis
 - Transparent tape is pressed against the perineum at night

- Identify eggs under the low-power lens of microscope (Fig. 16-12)
- Treatment: pyrantel and mebendazole

TRICHINOSIS

- *Trichinella spiralis*
- Larval cysts ingested from undercooked meat (usually pork)
- Acidity and enzymatic activity of the human digestive system disrupt the cyst, releasing large numbers of newborn larvae that penetrate the gut wall, enter the systemic circulation, and migrate to various tissues
- Larvae usually persist only in striated skeletal muscle cells, transformed into nurse cells
- Calcified cysts in muscle, elevated muscle enzymes
- Fever, myalgias, and periorbital edema (increased interstitial fluid)
- Vasculitis: splinter hemorrhages in nails and eyes
- Diagnosis
 - Enzyme immunoassay (EIA) or the bentonite flocculation (BF) test
 - Elevated creatine kinase (CK) and lactate dehydrogenase (LDH)
 - Stool examination: Charcot-Leyden crystals from eosinophils may be found in stools
- Treatment
 - Trichinosis is usually a self-limited illness
 - Prednisone
 - Mebendazole and albendazole
 - Proper cooking of meat is the most effective method to prevent infection

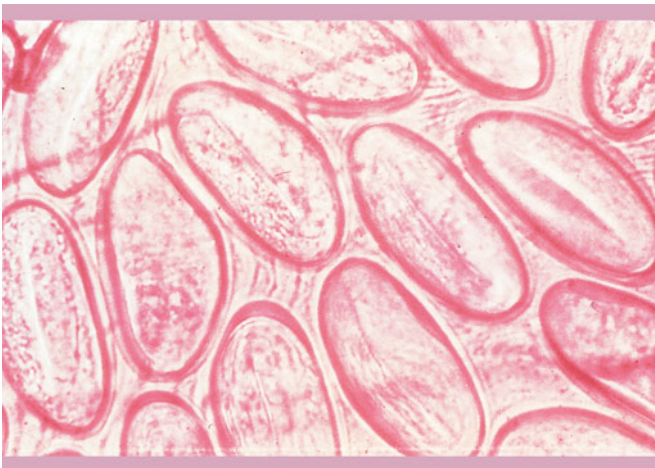


FIGURE 16-12 *Enterobius* eggs under the microscope. (From Freedberg IM et al. *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003, p. 2239.)

DRACUNCULIASIS

- *Dracunculus medinensis*, guinea fire worm; nematode
- Ingested larvae reside in an intermediate host, a tiny freshwater crustacean or copepod
- Migrates from the gastrointestinal tract to a location in the lower extremity (most commonly the foot), causing a bulla that ruptures to release the larvae back into water
- Clinical: presence of the adult worm in the subcutaneous tissue, usually lower extremity
- Constitutional symptoms
- Treatment
 - Slowly wind worm around stick
 - Metronidazole, thiabendazole may cause aberrant migration of worms, and should be used with caution.

FILARIAE

- Eight species of roundworm belonging to the family Filarioidea develop to adulthood in humans
- Larvae or microfilariae are ingested by a feeding insect vector
- Larvae are then inoculated into the vertebral host for the final stages of development
- Cutaneous group (listed below)
 - *Loa loa*
 - *Onchocerca volvulus*
 - *Mansonella streptocerca*
- Lymphatic group
 - *Wuchereria bancrofti*: causes Bancroftian filariasis
 - Genital disease: edema of scrotal skin, funiculitis, epididymitis, orchitis, and hydrocele
 - Distinctive lymphangitis of the arms or legs characterized by a unique retrograde spread or extension
 - Starting in a single node, erythematous patches of subcutaneous edema or diffuse erythema and edema develop and progress distally
 - Treatment: diethylcarbamazine, ivermectin
 - *Brugia malayi*: causes Malayan filariasis
 - *Brugia timori*: causes Timorian filariasis
 - Clinical manifestations of Malayan filariasis and Timorian filariasis:
 - Axillary or inguinal lymphadenitis, lymphangitis, and fever are common
 - Lymphatic abscesses and resulting scarring
- Body cavity group
 - *Mansonella streptocerca*: causes streptocerciasis
 - Central and West Africa
 - Transmitted by the midge *Culicoides grahami*
 - Adult worms are found in the dermis of the patient's upper trunk
 - Microfilariae are found in the dermis and lymph nodes
 - Treatment: diethylcarbamazine

- Loiasis (*Loa loa*)
- Vector: *Chrysops* (deer fly)
- Rain forests of Central and West Africa
- Diurnal periodicity: microfilariae are found in the bloodstream in highest numbers during the day
 - Clinical manifestations:
 - Transient, nontender areas of angioedema and urticaria are the major signs and symptoms
 - Calabar swellings: transient subcutaneous swellings on the extremities
 - Worm migration across conjunctiva or bridge of nose
 - Localized pain, pruritus, and urticaria
 - Arthritis, breast calcification, meningo-encephalopathy, endomyocardial fibrosis, peripheral neuropathy, pleural effusions, and retinopathy
- Treatment: diethylcarbamazine
 - Mazzotti reaction: stroke or meningoencephalitis from release of dead microfilariae in blood and cerebrospinal fluid (CSF) after treatment with diethylcarbamazine (DEC); it may occur without drug therapy
- Onchocerciasis (river blindness, hanging groins, leopard skin, or sowdah)
- *Onchocerca volvulus*
- Vector: *Simulium* species of blackflies
- Tropical Africa
- Microfilariae found in the dermis, eyes, and regional lymph nodes
- Clinical manifestations:
 - Pruritus, subcutaneous lumps, lymphadenitis, and blindness
 - Onchocercoma: Subcutaneous nodules common over bony prominences
 - Ocular: punctate keratitis, pannus formation, corneal fibrosis, iridocyclitis, glaucoma, choroiditis, and optic
 - “Lizard skin,” “hanging skin”: Fibrosis and atrophy may cause lymph nodes or portions of bowel to hang in pockets of skin
 - Hypopigmented patches in Africans (“leopard skin”)
 - Hyperpigmented patches in Arabics (sowdah)
 - Facial edema/pruritus in Mexico and Guatemala (erysipela de la Costa)
- Diagnosis
 - Slit-lamp examination: microfilariae in the eye
 - Biopsy of a nodule will reveal an adult worm
- Treatment: ivermectin
- Mansonelliasis
- Vectors: midge species *Culicoides austeni* and *Culicoides grahamei*
- *Mansonella streptocerca*
- Subcutaneous infection in humans

TOXOCARIASIS

- Visceral larva migrans
- Caused by the roundworm of the dog and cat: *Toxocara canis* and *T. cati*
- Eggs ingested from soil; larvae penetrate bowel and lodge in organs and blood vessels
- Hemorrhage, necrosis, urticaria
- Ocular larva migrans: penetrating larva can become encysted, leading to the formation of a large granuloma

GNATHOSTOMIASIS (WANDERING SWELLING, YANGTSE RIVER EDEMA)

- *Gnathostoma spinigerum*
- Humans eat fish that contain larvae, or larvae penetrate the skin directly
- Migrating erythematous swelling, pain, pruritus
- Treatment: surgery, ivermectin, albendazole

TREMATODES (FLUKES)

- Phylum Platyhelminthes contains the dorsoventrally flattened worms
- Schistosomiasis (bilharziasis)
- Life cycle
 - Eggs passed in urine (*S. haematobium*) or feces (*S. japonicum* and *S. mansoni*), hatch in water
 - From eggs, miracidia hatch into the water, where they penetrate into snails; in the snails they develop into cercariae that penetrate the host skin
 - Enter the portal venous system of the liver and travel to heart, lungs, and finally the bladder or the mesenteric vessels
- Schistosomiasis organisms (blood flukes)
 - *S. mansoni*
 - South America
 - Portal hypertension, found in large intestine and liver, eggs shed in stool
 - Location of spine on ova: lateral
 - *S. japonicum*
 - Asia
 - Portal hypertension; found in small intestine and liver; eggs shed in stool
 - Location of spine on ova: no spine
 - *S. haematobium*
 - Africa, Middle East
 - Found in bladder, pelvic/urogenital venules; eggs shed in urine
 - Location of spine on ova: apical
- Clinical
 - Cercarial dermatitis (swimmer’s itch):
 - Pruritus, dermatitis
 - Skin exposure to fresh or salt water
 - Macular eruption, pruritic
 - Spares clothing-covered skin

- Acute syndrome, Katayama fever: spiking afternoon fevers, chills, bronchitis, pneumonitis, headache, lymphadenopathy, hepatosplenomegaly, joint pain, diarrhea, urticaria, eosinophilia, leukocytosis, and an elevated erythrocyte sedimentation rate
- Late hypersensitivity reaction: generalized urticaria, pruritus, lichenified papules, or dermatographism
- Treatment: antihistamines plus topical steroids for itch, praziquantel

FASCIOLIASIS

- *Fasciola hepatica*
- Metacercariae on plants are ingested by sheep or humans; larvae migrate to the bile duct
- Hepatomegaly, right upper quadrant pain, jaundice, urticaria
- Treatment: surgery, bithionel, triclabendazole

CESTODA

Tape Worms

- Long, segmented worms
- Include
 - Cysticercosis
 - Echinococcosis
 - Sparganosis
 - Coenurosis
- Life cycle
 - Eggs passed from the primary host and ingested by an intermediate host, where eggs hatch
 - Larvae encyst within tissues
 - Infection of the primary host occurs by ingesting the cyst-infested flesh of the intermediate host

Cysticercosis

- *Taenia solium*
- Eggs in undercooked pork ingested and penetrate bowel to enter muscle, brain, and eyes where they develop into larvae
- Seizures, mass lesions, nodules
- Treatment: surgical excision, albendazole, praziquantel

Echinococcosis

- *Echinococcus* species (*E. granulosus*: dog; *E. multilocularis*: fox)
- Eggs from animal feces are ingested; larvae hatch and penetrate gut wall
- Hydatid cyst in the abdomen
- Treatment: surgical excision, mebendazole

Sparganosis

- *Spirometra* species
- Larvae from undercooked fish are ingested
- Enlarging subcutaneous nodule
- Treatment: surgical excision

Coenurosis

- *Taenia* species (multiceps, serialis, brauni)
- Eggs in host feces (dogs, fox, wolf)
- Ingested by herbivores (cows) and penetrate bowel to enter muscle, brain, and eyes, where they develop into larvae
- Seizures, mass lesions, subcutaneous nodules
- Treatment: surgical excision

REPTILES

Snakes

- United States: rattlesnake, cottonmouth moccasin, and copperhead (family *Crotalidae*) account for the vast majority of bites

ELAPIDAE FAMILY

- Coral snake
 - Round eyes
 - Red and yellow or white bands (“red on yellow kills a fellow” helps distinguish from milk snake)
 - Neurotoxic
 - Muscle fasciculations, later flaccid paralysis
- Viperidae family (pit viper)
 - Copperhead, rattlesnake, cottonmouth (water moccasin)
 - Triangular head distinct from the body
 - Elliptical “cat’s eye” pupils
 - Venom with hydrolases; anticoagulant in the venom causes hemolysis and capillary leakage
 - Pain, edema, ecchymosis, vesiculation, petechiae, and tissue necrosis can develop at the site of the bite
 - Damage to vascular endothelium, hypotension

QUIZ

Questions

1. Endemic typhus is carried by:
 - A. *Ctenocephalides felis*
 - B. *Tunga penetrans*
 - C. *Pulex irritans*
 - D. *Xenopsylla cheopis*
 - E. Both A and D

2. Body lice carry:
 - A. Epidemic typhus
 - B. Trench fever
 - C. Relapsing fever
 - D. Bacillary angiomatosis
 - E. All of the above
3. Leishmaniasis is carried by:
 - A. Sandflies
 - B. Mosquitoes
 - C. Deer flies
 - D. Ticks
 - E. Mites
4. The first stage of sleeping sickness is characterized by a (an):
 - A. Chancre
 - B. Buboe
 - C. Lymphadenitis
 - D. Persistent fever
 - E. Enlargement of the spleen
5. Mosquitoes carry:
 - A. Filariasis
 - B. Yellow fever
 - C. Dengue
 - D. Encephalitis
 - E. All of the above
6. Reduviid bugs transmit:
 - A. Chagas disease
 - B. Leishmaniasis
 - C. Dengue
 - D. Malaria
 - E. Sleeping sickness
7. Tick paralysis in North America is most closely associated with:
 - A. *Dermacentor* ticks
 - B. *Rhipicephalus* ticks
 - C. *Ornithodoros* ticks
 - D. *Amblyomma* ticks
 - E. *Ixodes* ticks
8. *Liponyssoides* mites carry:
 - A. Rickettsial pox
 - B. Typhus
 - C. Typhoid
 - D. Rocky Mountain spotted fever
 - E. Relapsing fever
9. *Cheyletiella* mites are associated with:

- A. Walking dandruff in dogs
- B. Mange in dogs
- C. Alopecia in hedgehogs
- D. Cat scratch disease
- E. Endemic typhus

10. *Ornithodoros* ticks are associated with:

- A. Relapsing fever
- B. Rickettsial pox
- C. Typhoid
- D. Typhus
- E. Colorado tick fever

Answers

1. E. While *Xenopsylla cheopis* has been considered the classic vector of endemic typhus, in recent years *Ctenocephalides felis* has been recognized as a major vector. The disease has emerged as more common in South Texas, where the vector is *C.felis* and opossums serve as a disease reservoir.
2. E. While head and pubic lice are not clearly linked to the spread of disease, body lice are important disease vectors, especially in refugee populations. They carry epidemic typhus, trench fever, relapsing fever, and the bacillary angiomatosis organism. When transmitted by a louse, the latter organism is more likely to cause endocarditis.
3. A. Leishmaniasis is carried by sandflies, *Phlebotomus* sp. in the old world and *Lutzomyia* species in the new world. Sandfly bites correspond to the site of ulcer or nodule formation.
4. A. The organisms that cause sleeping sickness are related to those that cause leishmaniasis. Both produce chancriform lesions. Sleeping sickness also causes urticaria, pruritus, facial edema, fever, and arthralgias, central nervous system manifestations occur in the second phase of illness.
5. E. Mosquitoes cause more human morbidity and mortality than any other group of arthropods. Among the many diseases they spread are filariasis, yellow fever, dengue, and viral encephalitis.
6. A. Chagas disease is transmitted by Reduviid bugs. Bedbugs may represent a secondary vector. Leishmaniasis and sleeping sickness are spread by biting flies and malaria and dengue are spread by mosquitoes.
7. A. In North America, *Dermacentor* ticks are the most important cause of tick paralysis. The ticks attach to the head and neck region and are often hidden by hair, contributing to the significant mortality associated with tick paralysis. *Ixodes* ticks cause tick paralysis in Australian dogs.

8. A. *Liponyssoides* mites carry rickettsial pox. Typhus is carried by lice, relapsing fever by lice and ticks, and Rocky Mountain spotted fever by ticks. Most typhoid is food-borne.
9. A. *Cheyletiella* mites affect cats, dogs and rabbits. They produce eczematous “hot spots” referred to as walking dandruff.
10. *Ornithodoros* ticks carry relapsing fever. Relapsing fever may also be louse-borne. Rickettsial pox is transmitted by a mite, typhus by a louse, and Colorado tick fever by *Dermacentor* ticks. Typhoid is most commonly food borne.

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VIRAL DISEASES

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DNA VIRUSES

1. Pox viruses
2. Papillomaviruses
3. Herpes viruses
4. Parvoviruses
5. Hepadnavirus

Pox Viruses

- Large, enveloped, double-stranded, linear DNA viruses
- Belong to the Poxviridae family
- Replicate in the cytoplasm, except for the adenovirus
- Poxviruses of clinical importance include: smallpox, vaccinia, monkeypox, molluscum contagiosum, orf and milker's nodules

MOLLUSCIPOX (MOLLUSCUM CONTAGIOSUM; MCV)

- Common, benign, self-limiting skin disease
- Generally affects pediatric age group
- Virus commonly acquired by skin to skin contact (non-sexual)
- Incubation period is from 2 weeks to 6 months
- Four different strains have been identified (based on restriction endonuclease digestion pattern). Two main subtypes: MCV I, responsible for the majority of infections in the United States, and MCV II (more prevalent in HIV patients); both are genital/nongenital
- Clinical
 - 3- to 6-mm erythematous or skin-colored, dome-shaped, umbilical papules distributed over the

trunk and face. The lesions may persist for six to eight weeks or more (Fig. 17-1)

- In immunocompromised patients, especially HIV-infected individuals, thousands of papules distributed on the body and face. High risk of bacterial infection and treatment resistance
- Genital papules: usually sexually transmitted, most common in adults (Fig. 17-2)
- Positive Koebner reaction
- Free virus cores found in all layers of epidermis
- Diagnosis
 - Clinical
 - Confirmatory biopsy in some cases. Henderson-Paterson bodies (molluscum bodies) = viral particles in infected keratinocytes, eosinophils
- Treatment
 - Resolution is often preceded by inflammation, uncomplicated lesions heal without scarring
 - Physical destruction (salicylic acid, liquid nitrogen, cantharidin, lactic acid, CO₂, trichloroacetic acid)
 - Immune modulation: imiquimod
 - Manual extrusion (curettage) of the lesions
 - Cidofovir in immunocompromised patients

SMALLPOX

- Caused by variola virus; variola minor also known as alastrim
- Serious, contagious, and sometimes fatal infectious disease
- Eradicated after a successful worldwide vaccination program
- Face-to-face contact is not required to be infected, direct contact with infected body fluids or contaminated objects



FIGURE 17-1 Molluscum contagiosum. (Courtesy of Dr. Adelaide Hebert.)

- Humans are the only natural host
- Clinical
 - Incubation 12 to 13 days, fever, malaise, backache, body aches and exanthem that appears after 2 to 4 days
 - Two clinical forms: *Variola major*, most common and severe form with a 30% incidence of mortality (secondary to pulmonary edema from heart failure) four clinical types: ordinary, modified (by previous vaccination), flat, and hemorrhagic and *Variola minor*, less severe and 1% mortality
 - Early rash appears as small red spots in the mouth; macules → papules → vesicles → pustules; all lesions exist in the same stage
 - Complications: corneal ulceration, laryngeal lesions, encephalitis, hemorrhage
 - Progressive vaccinia related to immunosuppression, malignancy, radiation therapy, or AIDS
- Vaccination: rare postvaccinal encephalitis and progressive vaccinia; high level immunity for 3 to 5 years and decreasing immunity thereafter
- Diagnosis
 - Clinical
 - Histology: balloon and reticular degeneration with hemorrhage inclusion bodies, polymorphonuclear cells
- Treatment
 - No antiviral treatment for smallpox; cidofovir suggested

VACCINIA (FIGS. 17-3 AND 17-4)

- Laboratory virus used to vaccinate against smallpox and monkeypox
- Infection occurs primarily in laboratory workers



FIGURE 17-2 Molluscum contagiosum genital. (Courtesy of Dr. Adriana Motta.)



FIGURE 17-3 Vaccinia. (Courtesy of Dr. Stephen Tyring.)



FIGURE 17-4 Vaccinia eye. (Courtesy of Dr. Stephen Tyring.)

- Congenital vaccinia infection of the fetus in the last trimester with cutaneous lesions (no other associated congenital abnormalities)
- Clinical
 - Vaccination reactions
 - Papule (3–4 days after vaccination)
 - Vesicle with surrounding erythema, umbilicated (5–6 days)
 - Pustule (8–9 days) confirms successful vaccination
 - Crust (12 + days)
 - Scar (17–21 days)
 - Systemic symptoms such as malaise, lymphadenopathy, myalgia, headache, chills, nausea, fatigue and fever may appear at day 8.
 - Usually self-limited except in immunocompromised individuals
 - Progressive vaccinia is one of the most severe complications (life threatening) of smallpox vaccination
 - Suspected when there is no evidence of normal resolution of the lesion at the vaccination site within 14 days and progression to central necrosis develops without surrounding erythema. Satellite and secondary lesions progress in the same fashion as the primary lesion
 - Systemic symptoms occur late in the onset of the disease, death occurs as a result of an overwhelming toxemia, viremia or septicemia
 - Cases in young children are due to a congenital immune deficiency. Adult cases are usually due to acquired immune suppression (HIV, cancer, immunosuppressive therapy)
- Treatment: vaccinia immune globulin (VIG) or surgical removal of massive lesions followed by VIG

MONKEYPOX

- Occasionally infects humans; predominantly residents of western and central Africa; vaccinia infection may confer protection
- Reported cases in the United States were related to direct contact with infected exotic or wild mammalian pets (prairie dogs)
- Clinical
 - Differs from the cases of monkey pox in Africa and the United States
 - Red erosion progresses to a white vesicle to an umbilicated pustule with a central hemorrhagic crust and satellite lesions
 - Dissemination may occur

COWPOX

- Infects cows, but more commonly seen in cats
- Cow/cat teats: sites of injury
- Lymphadenopathy, fever

ORF (ECTHYMA CONTAGIOSUM, SCABBY MOUTH)

- Large ovoid virus, 250×160 nm with surface tubules, resistant to drying
- Endemic among sheep and goats, oxen; infection from animals or fomites: barn doors, troughs
- Uncommon dermatosis resulting from cutaneous infection with sheep pox virus. Sheep farmers, veterinarians mainly affected
- Clinical
 - 4 to 7 days incubation followed by 36-day period with six clinical stages: each lasts 6 days
 - Lesions progress through several stages. They occur at sites of contact with infected animals or fomites
 - Papular stage: red elevated lesion
 - Target stage: nodule with red center, white ring, red halo
 - Acute stage: weeping surface
 - Regenerative stage: thin, dry crust with black dots
 - Papillomatous stage: small papillomas over surface of lesion
 - Regressive: thick crusts heal with scarring
- Systemic symptoms include lymphangitis, lymphadenitis, malaise and fever
- Diagnosis
 - Based on typical clinical skin lesion and a history of sheep exposure. It is confirmed by histological study with or without electron microscopy
 - Histology varies depending on the stage of the lesion. Epidermal necrosis is prominent with vacuolization of cells in the upper third of the stratum spinosum. Eosinophilic inclusion bodies in the cytoplasm and nucleus of infected cells and mixed infiltrate in the dermis
- Treatment
 - Spontaneous remission

MILKER'S NODULES (PARAVACCINIA)

- Paravaccinia virus is a 140×310 nm, double stranded DNA poxvirus
- It is resistant to desiccation, cold and heat
- Endemic to cattle, on cow teats
- Occupational disease affects mainly milkers, farm workers and veterinary surgeons
- Clinical
 - Incubation period varies from 4 days to weeks
 - Lesions usually found on the fingers, the hand or the forearm
 - One single lesion or few lesions (in burned areas), 0.5–1.5 cm in diameter, firm, dome-shaped, movable, red or purplish red papules or nodules, some may have a target like appearance and central ulceration may occur

- Nodules grow slowly and are asymptomatic, systemic symptoms are not common
- A milker’s nodule may not be clinically distinguishable from Orf lesions
- Lesions heal without scarring
- Diagnosis
 - Based on typical clinical skin lesion and a history of cow exposure
 - Histology: similar to Orf
- Treatment
 - Usually self-limited (i.e., spontaneous resolution)

Human Papillomaviruses (HPV)

- Non-enveloped, double-stranded, circular DNA viruses with approximately 8000 base pairs
- HPV genome encodes early proteins (E1–E7) and late proteins (L1–L2)
- Proteins E6 and E7 are involved in oncogenesis. E6 inactivates the tumor suppressor protein p53 blocking cell apoptosis. E7 inactivates the Rb-family proteins inducing cell proliferation
- Clinical
 - Infect epithelia or skin or mucosa and mostly causes benign papillomas or warts
 - Most infections are transient; however, lesions may recur, persist or become latent (especially in immunocompromised individuals)
 - Main risk factor is close personal contact, the lesions spread by direct skin to skin or skin to mucosa contact. Other factors involved are the quantity of HPV in the lesion, the type of contact, the immune status of the individual and the lesion location
 - Lesions may koebnerize

- HPV may cause genitomucosal lesions, nongenital cutaneous lesions, epidermodysplasia verruciformis (EV) and Heck’s disease
- Anti-viral treatments exist (Interferon, imiquimod–indirect action and cidofovir), but most therapies aim to destroy the clinical lesions

NONGENITAL CUTANEOUS DISEASES (TABLE 17-1)

- Occur in 10% of children, peak incidence between 12 and 16 years old, adults are also affected but less commonly
- The clinical lesions can be classified as:
 - Verruca palmaris or plantaris (myrmecia or palmoplantar wart) (Fig. 17-5)
 - Clinical
 - ▲ “Anthill” HPV1
 - ▲ Volar aspects of palms/soles, tips of fingers/toes
 - ▲ Thick, endophytic papules with a central depression
 - ▲ Pain with pressure when walking
 - Diagnosis
 - ▲ Histology: ortho- and parakeratosis, acanthosis and extensive papillomatosis. Rete ridges extend further into the dermis. Higher power intracytoplasmatic, eosinophilic, keratohyalin-like granules within the epithelial cell in the low stratum of malpighii
 - Verruca vulgaris (common warts)
 - HPV 1, 2 or 4
 - Clinical (Fig. 17-6)
 - ▲ Verrucous papules
 - ▲ The lesions can be hyperkeratotic, exophytic and dome-shaped papules

TABLE 17-1 Nongenital Cutaneous Disease

	HPV Type
Common warts (verrucae vulgaris)	1, 2, 4, 26, 27, 29, 41, 57, 65
Plantar warts (myrmecia)	1, 2, 4, 63
Flat warts (verrucae plana)	3, 10, 27, 28, 38, 41, 49
Butcher’s warts (common warts of people who handle meat, poultry, and fish)	7
Mosaic warts	2, 27, 57
Ungual squamous cell carcinoma	16
Epidermodysplasia verruciformis (benign)	2, 3, 10, 12, 15, 19, 36, 46, 47, 50
Epidermodysplasia verruciformis (malignant or benign)	5, 8, 9, 10, 14, 17, 20, 21, 22, 23, 24, 25, 37, 38



FIGURE 17-5 Plantar warts. (Courtesy of Dr. Stephen Tyring.)



FIGURE 17-6 Verrucae vulgaris. (Courtesy of Dr. Adrian Motta.)

or nodules with punctuate black dots (thrombosed capillaries and capillary bleeding)

- Treatment
 - ▲ Salicylic acid, 50% trichloroacetic acid, cantharidin, cryotherapy with liquid nitrogen, electrodesiccation, combination therapy using cryodestruction or surgery and imiquimod
- Verrucae plana (flat warts) (Fig. 17-7)
 - HPV 3 or 10
 - Clinical
 - ▲ Slightly elevated flat flesh-colored papules that may be smooth or slightly hyperkeratotic
 - ▲ Located on dorsal hands, arms or face, often in a linear array
 - Treatment: retinoic acid 0.05% applied daily until desquamation occurs; mild irritation may occur, imiquimod or a combination of the treatment options
- Butcher's warts
 - HPV7
 - Proliferative hand warts
 - Histology: same as common warts
- Epidermodysplasia verruciformis (EV)
 - Very rare chronic disease
 - Autosomal recessive pattern
 - Unique susceptibility to cutaneous infections by a group of phylogenetically related HPV types (mainly types 5 and 8)
 - Manifest at childhood
 - Clinical
 - ▲ Lesions are polymorphic, verruca plana-like, red-brown plaques



FIGURE 17-7 Verruca plana (flat warts). (Courtesy of Dr. Asra Ali.)

- ▲ Actinic keratoses arise after the age of 30 years and transform into bowenoid or squamous cell carcinomas (50% of patients)
- Diagnosis
 - ▲ Clinical confirmed by biopsy
 - ▲ Histology: stratum corneum with a basketweave appearance, uneven keratohyaline granules; large, coarse granules in the epidermis; koilocytes; gray cytoplasm; increase in amount of cytoplasm. Dysplasia and actinic keratoses may be evident

- Treatment
 - ▲ No effective treatment
 - ▲ Counsel patients to protect the skin from ultraviolet radiation exposure; radiation therapy is contraindicated in EV
 - ▲ Retinoids: long-term isotretinoin has been shown to decrease number of benign lesions and slow appearance of premalignant and malignant lesions
 - ▲ Imiquimod

ANOGENITAL DISEASE ASSOCIATED WITH HPV (TABLE 17-2)

- HPV infection is extremely common; the US has an annual incidence of approximately 5.5 million cases
- Risk factors include increased number of lifetime sexual partners
- HPV types involved are types 6, 11, 16 and 18
 - Condyloma acuminatum (anogenital warts) (Fig. 17-8)
 - 75% of sexually active adults will have an HPV infection, most subclinical, by age 50
 - The prevalence of anogenital HPV infection peaks in women age 25 with a second peak in women over the age of 55
 - HPV6 and HPV11 are the most common types of anogenital HPV
 - Less commonly HPV16, -18, -21, -22, and -55
 - Clinical
 - ▲ Flesh-colored to pink to reddish-brown, small, verrucous papules; discrete, sessile, smooth-topped papules or nodules or exophytic cauliflower-like lesions that usually are found near moist surfaces
 - ▲ Few centimeters in diameter but they may coalesce
 - ▲ Location: perianal area, crural folds, anus, rectum, urethra, vagina, cervix, labia, and vulva
 - Diagnosis
 - ▲ Histology: parakeratosis (mucosa), papillomatosis, acanthosis, elongated rete ridges, occasional mitotic figures. Koilocytes: dark nuclei with dyskeratosis
 - Treatment
 - ▲ Often challenging and may require multiple visits with more than one treatment sometimes necessary
 - ▲ Liquid nitrogen
 - ▲ Electrocautery
 - ▲ Curettage
 - ▲ Podofilox
 - ▲ Imiquimod cream 5%
 - ▲ Use of condoms may reduce transmission
 - ▲ Topical cidofovir (not FDA approved)
 - ▲ Topical kunecatechins ointment 15%

TABLE 17-2 Anogenital Diseases Associated With HPV

	HPV Type
Condyloma acuminata	6, 11, 30, 42, 43, 44, 45, 51, 52, 54
Bowenoid papulosis	16, 18, 34, 39, 42, 45
Bowen's disease	16, 18, 31, 34
Giant condyloma (Buschke-Löwenstein tumors)	6, 11



FIGURE 17-8 Anogenital disease. (Courtesy of Dr. Stephen Tying.)

- Bowenoid papulosis
 - Rare manifestation of HPV infection
 - HPV16, -18, and -33 (oncogenic)
 - Young, sexually active adults; cervix in females
 - Premalignant disease
 - Clinical
 - ▲ Red or hyperpigmented, multiple groups of well-demarcated, 2 to 3 mm papules on the external genitalia
 - Diagnosis
 - ▲ Clinically confirmed by histology
 - ▲ Histology: full-thickness dysplasia, dysplastic keratinocytes
 - Treatment
 - ▲ Cryotherapy, laser, excision, topical retinoids, 5-fluorouracil 5% solution, imiquimod 5% cream (studies show this treatment has a lower recurrence rate than other treatments)

- Premalignant and malignant diseases. Verrucous carcinoma (giant condyloma acuminata of Buschke and Lowenstein tumor)
 - Low grade squamous cell carcinoma
 - Infection with HPV6, HPV11 (types not usually associated with malignancy)
 - Clinical
 - ▲ Large exophytic tumors up to several centimeters in diameter
 - ▲ Locally invasive and destructive
 - ▲ Rarely metastasize
 - Treatment
 - ▲ Local excision
- Bowen's disease
 - Some cases associated with human papilloma virus
 - Clinical
 - ▲ Insidious onset, lesions have a slow rate of growth and are minimally symptomatic
 - ▲ Slightly raised plaque (sometimes misdiagnosed as eczema) with an irregular border and the surface can be fissured with adherent scales
 - Diagnosis
 - ▲ Histopathology: full thickness dysplasia of squamous epithelium
 - Treatment
 - ▲ Excision, curettage, cryosurgery, topical 5-fluorouracil and/or imiquimod
- Erythroplasia of Queyrat
 - Penile Bowen's disease
 - A squamous cell carcinoma in situ
 - Located on the glans under the foreskin of the uncircumcised penis
 - Clinical
 - ▲ Red plaques with a moist surface
 - ▲ Metastasis occur in 10% to 30%
 - Diagnosis
 - ▲ Histopathology: same as Bowen's above
 - Treatment
 - ▲ Excision, curettage, cryosurgery, topical 5-fluorouracil and/or imiquimod

NONGENITAL MUCOSAL DISEASE (TABLE 17-3)

- Oral focal epithelial hyperplasia (Heck's disease)
 - A rare disease
 - HPV types 13 and 32
 - Mostly affects the aboriginal population (i.e., Native American, Greenland, etc.)
 - Focal epithelial hyperplasia
 - Clinical
 - It affects the labial, lingual and buccal mucosa
 - Multiple flat-topped or dome-shaped pink-white papules, 1 to 5 mm, some lesions coalesce into plaques

TABLE 17-3 Nongenital Mucosal Disease

	HPV Type
Oral focal epithelial hyperplasia (Heck's disease)	13, 32
Oral carcinoma	16, 18
Oral leukoplakia	16, 18

- Diagnosis
 - Histology: hyperplastic mucosa with thin parakeratotic stratum corneum, acanthosis, blunting and anastomosis of rete ridges, pallor of epidermal cells as a result of intracellular edema
- Treatment
 - Surgical excision
 - Cryotherapy
 - Imiquimod 5% cream
 - Sulfonamides
 - Oral vitamin A

TREATMENTS FOR HPV

- Topical agents
 - Salicylic acid
 - Over-the-counter treatment
 - Removes surface keratin
 - Cantharidin
 - Dried extract of the blister beetle
 - Causes epidermal necrosis and blistering
 - Dinitrochlorobenzene (DNCB)
 - Powerful sensitizing agent
 - Induces an allergic contact dermatitis
 - Causes local inflammation and an immune response
 - Reported mutagen
 - Dibutyl squaric acid
 - Contact sensitizer
 - Unlike DNCB, it is not a mutagen and therefore may be a safer alternative
 - Trichloroacetic acid
 - Caustic compound
 - Causes immediate superficial tissue necrosis
 - Concentrations up to 80%
 - May require weekly applications
 - Podophyllotoxin
 - Derived from the roots of the Indian podophyllum plant
 - Binds to tubulin and prevents microtubule assembly

- Genital wart treatment: application twice daily for three consecutive days per week for up to 4 weeks
- Fluorouracil (5FU)
 - Used primarily to treat actinic keratoses
 - Antimetabolite: fluorinated pyrimidine
 - Active form inhibits DNA synthesis by inhibiting the normal production of thymidine
 - Effective in treating warts when used under occlusion daily for up to 1 month
 - Teratogenic
- Imiquimod 5% cream
 - Topical cream approved for treating genital warts; used for other HPV infections
 - Anogenital warts: treat at night, three times a week
 - Common warts: treat nightly under occlusion
 - Palmoplantar warts: treat nightly under occlusion, alternate with a keratolytic
 - Potent stimulator of proinflammatory cytokine release
 - Works best as part of combination therapy for nonanogenital warts
- Cidofovir
 - Nucleotide analogue of deoxycytidine monophosphate
 - Used for refractory condyloma acuminata and recurrent genital herpes
 - Cidofovir gel applied once or twice daily
 - Must be compounded
- Tretinoin
 - Disrupts epidermal growth and differentiation, thereby reducing the bulk of the wart
- Systemic agents
 - Cimetidine
 - Type 2 histamine receptor antagonist
 - Immunomodulatory effects
 - Variable results
 - 25 to 40 mg/kg tid \times 3 months
- Intralesional injections
 - Bleomycin
 - Cytotoxic polypeptide that inhibits DNA synthesis in cells and viruses
 - Side effects of bleomycin include pain with injection, local urticaria, Raynaud phenomenon, and possible tissue necrosis
 - If used periungually, bleomycin may cause nail dystrophy or nail loss
- Interferon-alpha
 - Recombinant version of naturally occurring cytokine with antiviral, anticancer, and immunomodulatory effects
 - Intralesional administration is more effective than systemic administration and is associated only with mild flu like symptoms.
 - Treatments may be required for several weeks to months before beneficial results are seen. Use for

warts that are resistant to standard treatments or use in combination therapy with surgery

- *Candida* antigen
 - Stimulates the acquisition of HPV immunity
 - Its application causes trauma and inflammatory reaction
- Cryosurgery: liquid nitrogen (-196°C) is the most effective method of cryosurgery
- Lasers
 - Carbon dioxide
 - Procedure can be painful and leave scarring
 - Risk of nosocomial infection also exists in health care workers because HPV can be isolated in the plume
 - Flashlamp-pumped pulse dye laser
 - Mixed results in treating warts
 - Decreased risk of scarring and transmission of HPV in the plume smoke
 - Electrodesiccation and curettage
 - May be more effective than cryosurgery
 - Painful
 - More likely to scar
 - HPV can be isolated from the plume
- Surgical excision: avoid using because of the risks of scarring and recurrence (or follow with interferon)

Human Herpes Viruses (HHV)

- Most herpes viruses measure approximately 200 nm in diameter
- Enveloped, linear, double-stranded DNA virus
- Biological features unique to herpes viruses are latency and reactivation
- Transmission: direct exposure of mucous membranes or abraded skin to the lesions or mucosal secretions of an infected individual or respiratory droplets
- Eight main types
 - HHV 1: herpes simplex 1 (HSV-1): herpes labialis > genitalis
 - HHV 2: herpes simplex 2 (HSV-2): herpes genitalis > labialis
 - HHV 3: varicella-zoster virus (VZV): chickenpox/herpes zoster
 - HHV 4: Epstein-Barr virus (EBV): mononucleosis, Gianotti Crosti, Burkitt's lymphoma, oral hairy leukoplakia
 - HHV 5: cytomegalovirus (CMV): retinitis in AIDS patients
 - HHV 6: roseola infantum (exanthem subitum)
 - HHV 7: possible pityriasis rosea
 - HHV 8: Kaposi's sarcoma

HERPES SIMPLEX VIRUS (HSV)

- **Herpes simplex 1 (HSV-1)**
 - Belongs to the family Herpesviridae
 - Humans are the only natural reservoirs, and no vectors are involved in transmission

- Eighty percent of U.S. adults are infected, 85% of adults infected worldwide
- Ninety percent orofacial, 10% genital
- Mode of transmission is by close personal contact
- Viral properties
 - Neurovirulence: capacity to invade and replicate in the nervous system
 - Latency
 - ▲ Establishment and maintenance of latent infection in nerve cell ganglia
 - ▲ HSV-1 infection: trigeminal ganglia are involved most commonly
 - ▲ Primary infection is subclinical (90%), gingivostomatitis (10%)
 - ▲ In 40% of HSV-1 seropositive persons recurrent herpes labialis usually recur one to four times per year
 - ▲ Accounts for 30% of primary but less than 5% of recurrent genital HSV
- Reactivation
 - Induced by a variety of stimuli: fever, trauma, emotional stress, sunlight, menstruation
 - Recurrent infection and peripheral shedding of HSV
 - Occurs more frequently in the perioral rather than the genital region
 - More frequent and severe in immunocompromised patients
- Clinical
 - Gingivostomatitis
 - ▲ Abrupt onset
 - ▲ Children aged 6 months to 5 years
 - ▲ High fever (102–104°F)
 - ▲ Anorexia and listlessness
 - ▲ Gingivitis is the most striking feature
 - ▲ Vesicular lesions develop on the oral mucosa, tongue, and or lips and later rupture and coalesce, leaving ulcerated plaques
 - ▲ Regional lymphadenopathy
 - ▲ Acute herpetic pharyngotonsillitis
 - ▲ Acute disease lasts 5 to 7 days
 - ▲ Viral shedding may continue for 3 weeks
 - Herpes labialis (Fig. 17-9)
 - Most common manifestation of recurrent HSV-1
 - Prodrome of pain, burning, and tingling often occurs at the site where lesions develop
 - Clinical
 - Erythematous papules develop rapidly into tiny, thin-walled, intraepidermal vesicles that become pustular and ulcerate
 - Maximum viral shedding is in the first 24 hours of the acute illness but may last 5 days



FIGURE 17-9 Herpes labialis. (Courtesy of Dr. Stephen Tying.)

- Diagnosis
 - Histology: acantholysis, intraepidermal vesicle, ballooning and reticular degeneration, intranuclear eosinophilic inclusion bodies, multinucleated keratinocytes (not specific)
 - Viral culture
 - Polymerase chain reaction (PCR) techniques: detection of HSV DNA
 - Immunofluorescent staining of the tissue culture cells or of smear can quickly identify HSV and can distinguish between types 1 and 2
 - Antibody testing
 - Tzanck smear: multinucleated giant cells → nucleus divides but not cell; nuclear molding; does not distinguish between HSV2 and VZV
- Treatment: see HSV-2 below
- **Herpes simplex 2** (HSV-2) (Figs. 17-10, 17-11, and 17-12)
 - Primary genital herpes; asymptomatic in most patients
 - Causes 70% of primary, > 95% of recurrent genital herpes
 - Women have 45% higher risk of infection compared to men
 - Primary infection asymptomatic: 75%
 - Ninety-five percent of asymptomatic females and males actively shed virus at some point in time
 - Eighty percent of transmission is secondary to asymptomatic shedding
 - Ninety percent have recurrences
 - Clinical
 - Incubation period is 3 to 7 days
 - Cervical vesicles resulting in ulcers; can recur with or without external lesions
 - Ulcerative lesions persist from 4 to 15 days
 - Viral shedding lasts approximately 12 days



FIGURE 17-10 Primary genital herpes. (Courtesy of Dr. Stephen Tying.)



FIGURE 17-11 Genital herpes. (Reprinted with permission from Wolff K, Johnson RA, Summmond D: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill; 2005.)



FIGURE 17-12 Herpes simplex type 2 (HSV-2). (Courtesy of Dr. Stephen Tying.)

- Systemic complaints in > 70% of primary HSV: fever, dysuria, malaise, lymphadenopathy, females greater than males
- Spread by sexual contact (1% to 2% days/year male, 6% to 8% female: asymptomatic transmission)
- Treatment
 - Acyclovir:
 - ▲ First episode: 200 mg five times daily or 400 mg tid for 7 to 10 days
 - ▲ Recurrences: 200 mg PO five times daily or 400 mg tid for 5 days
 - ▲ Chronic suppressive therapy: 400 mg bid or 200 mg three to five times daily
 - Valacyclovir (Valtrex)
 - ▲ First episode 1 g bid for 10 days
 - ▲ Recurrences: 500 mg twice daily for 3 days or 2 g bid for one day
 - ▲ Suppressive dosing for HSV: 500 mg to 1 g/d
 - Famciclovir (Famvir)
 - ▲ First episode: 250 mg tid for 10 days
 - ▲ Recurrences: 125 mg twice daily for 5 days or 1 gm (for genital herpes) or 1.5 once for herpes labialis
 - ▲ Suppression: 250 mg bid
- Herpes simplex virus in immunosuppressed patients
 - HIV: 95% coinfectd with HSV-1/HSV-2 or both
 - Fifty-two percent of HIV infections are among people who also have herpes simplex virus type 2

- Clinical
 - ▲ Recurrent HSV may last much longer compared with immunocompetent hosts (> 30 days)
 - ▲ Chronic ulcerative HSV: persistent ulcers and erosions starting on the face or perineal region

- ▲ Generalized acute mucocutaneous HSV: dissemination and fever after localized vesicular eruption
 - ▲ Systemic HSV: follows oral or genital lesions; areas of necrosis in the liver, adrenals, pancreas
- Treatment of genital ulcers caused by HSV-2 with specific antivirals has been previously shown to reduce HSV-2 and HIV shedding
- Acyclovir-resistant HSV in HIV patients (5–8%)
 - ▲ 1% Cidofovir (compounded)
 - ▲ Foscarnet
 - △ Reversibly inhibits viral DNA polymerase
 - △ Does not need thymidine kinase
 - △ Side effects: penile ulcers, nephrotoxicity
- Other herpes manifestations
 - Herpetic whitlow
 - HSV of the fingers, occurs at or near the cuticle or at other sites associated with trauma
 - HSV-2 > HSV-1
 - Herpes gladiatorum (Fig. 17-13)
 - Due to direct skin-to-skin contact among wrestlers
 - Scattered cutaneous HSV-1 lesions
 - Herpes-associated erythema multiforme (EM)
 - 80% of recurrent EM are thought to be associated with HSV reactivation
 - Multiple outbreaks of EM often associated with herpes reactivation
 - Pathogenesis may represent a delayed-type hypersensitivity reaction
 - Patients experience an average of 6 attacks annually, each episode lasting nearly 2 weeks
 - Self-limited
 - Herpetic keratoconjunctivitis
 - Recurrent erosions of the conjunctiva and cornea that can lead to blindness
 - Lumbosacral herpes simplex virus
 - Infection is typically asymptomatic but can cause sciatica
 - Eczema herpeticum (Fig. 17-14)
 - Widespread HSV infection in patients with skin disorders such as atopic dermatitis, Darier's disease, pemphigus, thermal burns or Sézary syndrome
 - HSV encephalitis (usually HSV-1)
 - Most common cause of sporadic encephalitis
 - Sudden onset of fever, headache, confusion, temporal lobe involvement
 - Seventy percent mortality if not treated
 - Ramsay Hunt (usually VZV or HSV-1)
 - Infection of the facial nerve



FIGURE 17-13 Herpes gladiatorum. (Reprinted with permission from Wolff K, Johnson RA, Summmond D: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill; 2005.)

- Symptoms on the affected side typically include facial weakness and a painful herpes-type skin eruption on the pinna of the ear, and there is frequently vestibulocochlear disturbance
 - Recovery of facial movement occurs in about 50% of treated patients
- Congenital herpes simplex virus
 - One in 3500 vaginal births
 - Transmission:
 - Perinatal: 90%; congenital: 5% to 8%; few postnatal



FIGURE 17-14 Eczema herpeticum. (Courtesy of Dr. Adelaide Hebert.)

- Risk of transmission: 50% if mother has primary infection, 3% to 5% if mother has recurrent disease
- Birth canal transmission: lesions usually on scalp, face; associated encephalitis, hepatorenal necrosis, pneumonia, death
- If transmission in first 8 weeks, severe defects result
- If lesions on infant in first 10 days, mortality is 20%
- Mortality rate (if no treatment) is 65% transplacental, 80% HSV-2, 20% HSV-1
- Treatment / prevention
 - Pregnancy
 - ▲ In infected females, initiate treatment at week 36 and continue until delivery:
 - △ Valacyclovir 1 g qd or
 - △ Famciclovir 250 mg bid or
 - △ Acyclovir 400 mg bid tid or 200 mg three to five times daily
 - IV acyclovir for neonates: 30 mg/kg per day
- **Varicella-zoster virus** [human herpes virus 3 (HHV 3)]
 - 98% of the adult population in the United States have serological evidence of previous infection
 - Causes chickenpox and herpes zoster
 - Chickenpox (Fig. 17-15)
 - Transmitted to others from the skin and respiratory tract
 - VZV remains dormant in sensory nerve ganglia after primary infection
 - Low-grade fever precedes skin manifestations by 1 to 2 days
 - Incubation period of about 2 weeks
 - Clinical
 - ▲ Prodromal symptoms include headache, myalgias, anorexia, nausea and vomiting



FIGURE 17-15 Chickenpox in adult. (Courtesy of Dr. Adrian Motta.)

- ▲ Lesions: “dewdrops on a rose petal”; begin on face, scalp, trunk, with relative sparing of the extremities
- Lesions start as red macules and pass through the stages of papule, vesicle, pustule, and eventually crust. Lesions are pruritic
- Different stages of the rash are present simultaneously
- Complications
 - ▲ Young immunocompetent individuals: secondary bacterial infection (*Staphylococcus aureus* or *Streptococcus pyogenes*) and scarring
 - ▲ Adults and immunocompromised: myelitis, large vessel granulomatous arteritis, encephalitis, varicella pneumonia or varicella hepatitis
- Congenital varicella syndrome
 - First 20 weeks of pregnancy: 2% risk of complications

- Leads to intrauterine growth retardation, microcephaly, cortical atrophy, limb hypoplasia, microphthalmia, cataracts, chorioretinitis, cortical atrophy and cutaneous scarring (areas of hypertrophic scarring with indurations and erythema located primarily on the extremities)
- Perinatal infection occurs within 10 days of birth
- If female gets VZV five days before or two days after delivery, the rate of mortality is 30%
- Infantile zoster
 - Manifests within the first year
 - Maternal varicella infection after the twentieth week of gestation
 - ▲ Neonatal varicella
 - Any infant with clinical or laboratory-confirmed varicella
 - Onset in the first month of life
 - ▲ Without features of varicella embryopathy
 - ▲ Infection may result from peripartum maternal infection or postnatal exposure
 - Treatment
 - ▲ Healthy children do not necessarily require acyclovir, but treatment allows them to return to school sooner
 - ▲ Acyclovir: 20 mg/kg; given orally four times daily for 5 to 7 days
 - ▲ Avoid aspirin to prevent Reye's syndrome
 - ▲ Symptomatic care
 - ▲ Adults
 - △ Acyclovir, famciclovir, valacyclovir at herpes zoster doses
 - △ Most effective if it is started within the first 72 hours after development of vesicles
 - Varicella vaccine
 - ▲ Two doses, at 12 months and 4–6 years of age
 - ▲ Seroconversion: adolescents and adults have a 78% conversion rate after the first dose and 99% after the second dose
- Zoster (shingles) (Fig. 17-16)
 - Due to reactivation of latent VZV in sensory ganglion (20% incidence unless immunocompromised)
 - Incidence: 66% of cases occur in patients older than 50 years
 - Clinical
 - ▲ Rash preceded by prodrome: fever, malaise, headache, localized pain in the involved dermatome
 - ▲ Constitutional symptoms develop initially



FIGURE 17-16 Zoster (shingles). (Courtesy of Dr. Adriana Motta.)

- ▲ Rash is in a unilateral dermatomal distribution with erythema, vesicles, pustules, & crusting
- ▲ Contagious until crusted
- ▲ Hutchinson sign: zoster on tip of nose (ophthalmic nerve, nasociliary division), could result in herpetic keratitis
- Complications
 - ▲ Postherpetic neuralgia (PHN)
 - △ Pain following resolution of skin

- lesions; occurs in 10% to 15% of patients; Resolution rate is 50% by 3 months, 75% by 1 year
 - △ Occurs in 60% of patients over age 60
 - ▲ Zoster sine herpete: segmental pain without lesions
 - ▲ Ophthalmic zoster: ocular disease (20% to 70% of cases with V-1 Zoster), cicatricial lid retraction, ptosis, keratitis, scleritis, uveitis, secondary glaucoma, oculomotor palsies, chorioretinitis, optic neuritis, panophthalmitis
 - ▲ CNS zoster: has asymptomatic cerebrospinal fluid (CSF) changes
 - ▲ Primary varicella pneumonia: 14%, higher rate in adults and immunocompromised patients
 - ▲ Reye's syndrome: acute fetal encephalopathy associated with fatty degeneration of the liver, associated with aspirin treatment
 - ▲ Bacterial superinfections: usually due to *Staphylococcus aureus*
 - ▲ Acute cerebellar ataxia: unsteady gait 11 to 20 days following rash
 - ▲ Guillian-Barré syndrome
 - △ Acute idiopathic polyneuritis
 - △ Encephalitis with headache, fever, photophobia, nausea, vomiting, nerve palsies
 - △ Motor paralysis (1% to 5%), extension from sensory ganglion to anterior horn, first 2 to 3 weeks
 - △ Ramsay Hunt: facial palsy secondary to herpes-zoster infection of facial (VII) and auditory (VIII) nerves; affects external ear, tympanic membrane; causes tinnitus, vertigo, deafness, otalgia, loss of taste
- Diagnosis
 - ▲ Nonspecific tests
 - △ Tzanck smear: multinucleated giant cells, nuclear molding
 - △ Histology: intraepidermal vesicles, balloon degeneration, reticular degeneration, inclusion bodies, margination of chromatin, vascular involvement (75% VZV)
 - ▲ Specific tests
 - △ Viral culture
 - △ PCR
- Treatment
 - ▲ Acyclovir: 800 mg five times daily for 7 days
 - ▲ Valacyclovir: 1 g three times daily for 7 days
 - ▲ Famciclovir: 500 mg three times daily for 7 days
 - ▲ Pain and pruritus: analgesics, oral antipruritics, calamine lotion, cool compresses
- Treatment of PHN
 - ▲ Non-narcotic or narcotic analgesic
 - ▲ Capsaicin cream
 - ▲ Topical lidocaine gel or patch
 - ▲ Tricyclic antidepressants: (amitriptyline, maprotiline, desipramine)
 - ▲ Anticonvulsants: carbamazepine, gabapentin, pregabalin
 - ▲ Sympathetic nerve blockade
 - ▲ Steroids: methylprednisolone
 - ▲ Transcutaneous electrical stimulation
- Vaccine: to increase immunity in persons seropositive for VZV in order to decrease risk of zoster. FDA approved for 60 years and older
- **Epstein-Barr virus** [human herpes virus 4 (HHV 4)]
 - Double-stranded DNA virus
 - Replicates in the nucleus
 - Primarily infects B-lymphocytes
 - After acute infection, EBV persists as a latent infection for life
 - Clinical
 - Infectious mononucleosis (IM)
 - ▲ Delayed primary infection with EBV
 - ▲ Young adults are typically affected and a small percentage of children and older adults contract the disease
 - ▲ Clinical
 - △ IM can be asymptomatic or have non-specific symptoms; the incubation period varies from 4 to 6 weeks
 - △ More frequent symptoms are a triad of fever, sore throat, lymphadenopathy (5% to 15%)
 - △ Rash: maculopapular (3% to 15% of patients)
 - △ Eighty percent of patients have rash if treated with amoxicillin or ampicillin
 - △ The resolution of the illness occurs between week 5 and 10
 - Diagnosis: see diagnosis of EBV on p. 300
 - Treatment: supportive care, antipyretics, analgesics, topical steroids for cutaneous manifestations. Prednisone for complications such as hemolytic anemia, thrombocytopenia, or lymphadenopathy that compromises the airway
 - Gianotti-Crosti (infantile papular acrodermatitis)
 - ▲ Self-limited cutaneous response to viral infections with worldwide distribution

- ▲ Most often in young children (between 6 months and 14 years of age)
- ▲ Clinical
 - △ Upper respiratory syndrome
 - △ Mild systemic compromise such as low-grade fever
 - △ Inguinal and axillary lymphadenopathy and hepatosplenomegaly
 - △ Symmetric cutaneous lesions appear abruptly: exanthem with monomorphic, edematous, pink-red papules or papulovesicles, slightly pruritic and can become confluent lichenoid papules that spare the trunk
 - △ Located on cheeks, buttocks and extensor surface of the extremities
 - △ Also associated with hepatitis B, adenovirus, CMV
 - △ Spontaneous resolution within three to four weeks
 - △ Treatment: supportive measures
- Oral hairy leukoplakia
 - ▲ Benign EBV infection of oral mucosa epithelial cells
 - ▲ Usually associated with immunocompromised patients
 - ▲ Prevalence of the disease amongst immunocompromised patients varies between 3% and 11%
 - ▲ Secondary nonmalignant hyperplasia of epithelial cells
 - ▲ Clinical
 - △ Location: lateral and dorsolateral parts of the tongue
 - △ Flat lesion with white corrugate vertical folds or ridges that cannot be scraped off
 - △ Self-limited course with resolution within months in immunocompromised persons
 - ▲ Diagnosis
 - △ Made clinically; confirmed with biopsy
 - △ Histology: hyperplasia, parakeratosis, acanthosis and papillated epithelial surfaces. EBV detected within ballooned and nonballooned cells of the prickle cell layer and the keratinized cells of the superficial epithelium
- Kikuchi's syndrome
 - ▲ Benign, self-limiting disease that resolves spontaneously within 1 to 4 months of onset
 - ▲ More common in Asia and usually affects young women in their late 20s and early 30s
- ▲ Pathology is suggestive of hyperimmune reaction to an infectious agent causing regional lymph node enlargement
- ▲ Clinical
 - △ Fever and leukopenia (50%), cervical lymphadenopathy
 - △ Mucocutaneous (16% to 40%) lesions: facial erythema, erythematous papules, plaques, nodules, cutaneous ulcers, and oral mucosal ulcers
- ▲ Diagnosis
 - △ Histology: histiocytic aggregates, atypical lymphoid cells, karyorrhectic debris, and patchy necrosis
- Plasmablastic Lymphoma
 - ▲ Recently discovered AIDS-related non-Hodgkin's lymphoma associated with chronic EBV infection
 - ▲ Usually affects the oral cavity, especially the gingival mucosa, hard palate, and soft palate
 - ▲ Infiltrates the mucosal surface, the adjacent bone, and finally the bone marrow, which usually occurs during therapy
 - ▲ Clinical
 - △ Similar to Kaposi's sarcoma: painful, purple red mass in the oral cavity, usually the gingival mucosa
 - △ Prognosis is poor with death occurring between 1 and 24 months after diagnosis
- Burkitt's lymphoma
 - ▲ Highly aggressive and poorly differentiated B-cell lymphoma with a high proliferative rate
 - ▲ EBV genome can be detected in tumor cells
 - ▲ Two types described (*i*) the endemic, or African BL (most often associated with EBV infection), and (*ii*) the sporadic
 - ▲ BL arises in the lymph nodes, nasopharyngeal mucosa, and the gastrointestinal tract
 - ▲ Cutaneous involvement is rare, only a few cases reported
 - ▲ Skin lesions include erythematous firm nodules in connection with the involved lymph node
- Nasopharyngeal carcinoma
 - ▲ Lymphoepithelial carcinoma with distinct histological types characterized by either squamous, non-keratinizing, or undifferentiated epithelial cells
 - ▲ Prevalent disease in southern China and Southeast Asia

- ▲ Patients have high levels of antibodies to EBV antigens
 - ▲ EBV genome is present in nasopharyngeal carcinoma cells
- Diagnosis of EBV
 - ▲ Leukocytosis
 - ▲ Lymphocytosis
 - ▲ Elevated liver function tests
 - ▲ Heterophile antibody test
 - △ Polyclonal secretion of antibodies by infected B cells
 - △ Heterophile test: nonspecific antibodies that agglutinate horse or sheep erythrocytes; heterophile antibodies may persist for 3 months after onset of illness
- Monospot test: measures acute infectious mononucleosis heterophile antibodies in a rapid qualitative fashion
- EBV serology
 - Major viral antigens:
 - Latent = EBNA → EBV nuclear antigens
 - Early = EADR → early antigen, diffuse restricted
 - Late = VCA → viral capsid antigen, MA → membrane antigen
- Treatment
 - Most EBV infections are self-limited; treat symptomatically
 - Oral hairy leukoplakia: acyclovir 400 mg five times daily
- **Cytomegalovirus (CMV)** [human herpes virus 5 (HSV-5)]
 - Enveloped double-stranded DNA virus restricted to humans
 - Transmitted through infectious secretions
 - In developing countries, 100% of the population is seropositive, 50% in developed countries
 - Latent infection in the host occurs after infection
 - Clinical
 - Primary infection
 - ▲ Usually asymptomatic in immunocompetent subjects
 - ▲ When symptomatic, it is called CMV mononucleosis syndrome
 - △ Fever, fatigue and less commonly lymphadenopathy, sore throat and organomegaly
 - △ One third have a maculopapular generalized rash
 - Primary infection in pregnant women
 - ▲ Occurs during the first trimester: rate of transmission is 40%
 - ▲ Most common congenital viral infection (1% of U.S. infants)
- ▲ A threat to the fetus
 - ▲ Congenital malformations: central nervous system injury, sensorineural hearing loss, growth retardation, microcephaly, cerebral atrophy, periventricular calcifications, chorioretinitis, thrombocytopenia and hepatosplenomegaly
 - ▲ Cutaneous manifestations: jaundice, purpuric macules and papules (secondary to persistent hematopoiesis – “blueberry muffin baby”)
- Immunocompromised patients
 - ▲ Retinitis, hepatitis and colitis
 - ▲ Skin lesions: vary from vesicles to verrucous plaques, and ulcerations in the perianal area
- Complications
 - CMV pneumonia (19%)
 - Mononucleosis-like syndrome after treatment with ampicillin or amoxicillin
 - Guillain-Barré syndrome
 - Bone marrow transplant patients have highest mortality (85%) secondary to pneumonia
 - Four times higher mortality rate than for solid-organ transplant
- In pregnant women, after the first trimester, hepatitis, pneumonia, purpura, and DIC may occur
- HIV and CMV: retinitis is the most common symptom
- Diagnosis
 - Histology: vasculitis, “owl’s eyes”: basophilic intranuclear inclusions
 - CMV antibodies
 - Antigenemia
 - Shell vial assay
- Treatment
 - Ganciclovir: drug of choice for treatment of CMV disease
 - Valganciclovir, prodrug of ganciclovir
 - Foscarnet: treats virus that is resistant to ganciclovir and valganciclovir
 - Cidofovir: treatment of refractory CMV retinitis
 - Fomivirsen
- **Human herpes virus 6 (HHV 6)**: roseola infantum (exanthema subitum/sixth disease) (Fig. 17-17)
 - Enveloped DNA virus
 - Spread by oropharyngeal secretions
 - Most common childhood exanthem
 - Clinical
 - Occurs most commonly in children aged six months to 2 years
 - Incubation: 5 to 15 days
 - Spread of infection during the febrile and viremic phase of the illness



FIGURE 17-17 Roseola infantum. (Courtesy of Dr. Stephen Tying.)

- Abrupt onset with high fever (102.2 to 105.8°F)
- Bulging anterior fontanelle, tonsillar and pharyngeal inflammation, tympanic injection, and lymph node enlargement
- Fever defervesces on the fourth day, coinciding with onset of a rash
- Rash: starts on trunk and may spread to neck and upper and lower extremities
- Pink macules: 2 to 5 mm
- May present with upper respiratory infection, adenopathy, central nervous system involvement, intussusception, thrombocytic purpura, palpebral edema (Berliner's sign, "heavy eyelids") and periorbital edema and mononucleosis like (as in adults). Seizures (6% to 15%) during the febrile phase
- Course: no sequelae generally observed
- HIV + HHV 6: tropism for CD4⁺ cells; upregulation of CD4 expression, which is needed by the gp120 unit of HIV to infect cells
- Bone marrow transplant patients: idiopathic bone marrow suppression secondary to virus
- **Diagnosis**
 - PCR
- **Treatment**
 - Symptomatic; a few case reports describe foscarnet and/or ganciclovir to be successful, but dosages are not known
- **Human herpes virus 7 (HHV 7)**
 - Significant homology with HHV 6
 - No clinical disease has been definitively linked to HHV 7; with questionable relationship to pityriasis rosea
 - Eighty-five percent of adults are seropositive, and most infections develop within the first 5 years of life

- Transmitted through saliva
- Diagnosis
 - Serology
- Treatment
 - Symptomatic
- **Human herpes virus 8 (HHV 8): Kaposi sarcoma (KS)** (Figs. 17-18 and 17-19)
 - Malignancy of lymphatic endothelial cells associated with human herpes virus 8
 - Four types
 - Endemic African KS: 50% of all childhood soft tissue tumors, usually an aggressive course
 - Epidemic AIDS-related KS: patients with advanced HIV infection
 - Immunocompromised (iatrogenic) KS: patients receiving immunosuppressive therapy; visceral involvement
 - Classic KS: sporadic and slowly progressive in 50–70 year-old men of Mediterranean and Eastern European background
 - Clinical
 - Brown, pink, red or violaceous macules/patches, papules/plaques, nodules. The lesions can vary depending upon the clinical variant
 - Mucous membrane, cutaneous and visceral involvement is common (lymph nodes, gastrointestinal tract and lungs)
 - Diagnosis
 - Biopsy: spindle cells, prominent slitlike vascular spaces, and extravasated red blood cells
 - Treatment
 - Antiretroviral therapy for epidemic AIDS-related KS



FIGURE 17-18 Kaposi sarcoma (classic). (Courtesy of Dr. Stephen Tying.)



FIGURE 17-19 Kaposi sarcoma (scrotal in patient with AIDS). (Courtesy of Dr. Stephen Tying.)

- Solitary KS lesions may be excised surgically or removed using laser surgery for patients with single lesions
- Radiation
- Combination of topical retinoids, intralesional vinblastine, interferon- α and chemotherapy: liposomal doxorubicin, liposomal daunorubicin, vincristine, vinblastine, bleomycin, and paclitaxel
- Herpes virus B: herpes simiae
 - Macaque herpes virus that is occasionally transmitted to humans from a bite, scratch, or open wound
 - Neurotropic: remains latent in ganglia
 - Clinical
 - In humans: initial local erythema, vesicular eruption with constitutional symptoms
 - Death secondary to encephalitis; very high mortality rate
- Treatment: nucleoside analogues (e.g., intravenous acyclovir)

Parvoviruses

PARVOVIRUS B19: “SLAPPED CHEEKS,” FIFTH DISEASE, ERYTHEMA INFECTIOSUM (FIG. 17-20)

- Single stranded DNA erythrovirus
- Tropism for rapidly dividing erythrocyte precursors
- Clinical
 - Twenty percent are asymptomatic
 - Headache, coryza, and low-grade fever about 2 days prior to the onset of the rash
 - Characterized by a “slapped cheek” appearance of the face on the first day
 - Erythematous, lacy macular eruption on the trunk and extremities
 - After rash fades, a lacy marble-like pattern to the skin appears: not contagious at this stage
 - Eruption can last 5 to 9 days and can recur for weeks or months with triggers such as sunlight, exercise, temperature change, bathing, and emotional stress
 - Headache, pharyngitis, fever, malaise, myalgias, arthralgias, coryza, diarrhea, nausea, cough, and conjunctivitis
 - Papular-pruritic “gloves-and-socks” syndrome: Erythematous exanthem of the hands and feet with a distinct margin at the wrist and ankle joints is present along with pain and edema
 - Complications: aplastic crisis in patients with increased red blood cell turnover, chronic anemia in immunocompromised persons, patients with chronic hemolytic anemia, fetal hydrops, sickle cell anemia, G6PD deficiency, and β -thalassemia



FIGURE 17-20 Parvovirus B19. (“slapped cheeks”). (Courtesy of Dr. Stephen Tying.)

- Diagnosis
 - Parvovirus serology (IgM and IgG) can be determined
 - PCR
 - Complete blood count (CBC): low reticulocyte count (0% to 1%)
- Treatment
 - Ibuprofen or acetaminophen for fever (to prevent Reye's syndrome: aspirin use is contraindicated)
 - Red blood cell (RBC) transfusions for aplastic crisis

Hepadna Viruses

HEPATITIS B

- Hepadna virus
- Partially double-stranded circular DNA
- Encodes four overlapping open reading frames as follows:
 - S for the surface or envelope gene encoding the pre-S1, pre-S2, and S protein
 - C for the core gene, encoding for the core nucleocapsid protein and the e antigen
 - X for the X gene encoding the X protein
 - P for the polymerase gene, encoding a large protein promoting priming, RNA-dependent and DNA-dependent DNA polymerase and RNase H activities
- Transmitted sexually, perinatally and through contact with body fluids
- Clinical
 - Incubation approximately 75 days
 - Prodromal or preicteric phase: serum sickness-like; develops in 20% to 30% of patients: arthropathy, proteinuria, hematuria
 - Icteric phase: jaundice (10 days after the appearance of constitutional symptomatology and lasts for 1 to 3 months), nausea, vomiting, and pruritus
 - Skin: urticaria/vasculitis secondary to perivascular deposition of immune complexes, hepatitis B + C3, IgM, or IgG
 - Associated conditions
 - Transient hypocomplementemia associated with urticaria
 - Polyarthritides nodosa: associated with arthralgias, fever, malaise, renal disease, nodules
 - Globulinemia: associated with chronic HBV, purpura, arthropathy, renal disease, necrotizing vasculitis, with mixed IgG and IgM
 - Others: erythema nodosum, urticaria, lichen planus, leukocytoclastic vasculitis, Gianotti-Crosti
- Diagnosis
 - Active hepatitis B: high levels of alanine aminotransferase (ALT) and aspartate

aminotransferase (AST); HBsAg (Australian antigen) and HBeAg (marker of infectivity) identified in the serum; HBcAb (IgM)

- Chronic inactive hepatitis B: HBsAg, HBcAb of IgG type, and HBeAb also are present in the serum
- Chronic active hepatitis B: mild to moderate elevation of the aminotransferases
- Treatment
 - Interferon- α
 - Lamivudine
 - Adefovir dipivoxil, entecavir, telbivudine, among others
- Hepatitis B vaccine available

RNA VIRUSES

1. Picornavirus
2. Paramyxovirus
3. Togavirus
4. Flavivirus
5. Retrovirus
6. Arenavirus: Lassa fever, Argentine hemorrhagic fever, and related viruses
7. Bunyavirus: ssRNA enveloped viruses, sandfly fever virus and Hantaan virus

Picornaviruses

- Nonenveloped (naked virions)
- Size range of 20 to 25 nm
- Capsids composed of four different proteins
- Genome is single-stranded (ss) RNA
- Size range of 7500 to 8500 nucleotides
- Three major human genera
 - Rhinoviruses
 - Hepatovirus: hepatitis A virus (HAV)
 - Enteroviruses
 - Poliovirus
 - Enterovirus
 - Coxsackie virus
 - Echovirus

ENTEROVIRUSES

- These are distinguished by other members of the Picornaviruses by its stability at low pH levels
 - Hand, Foot, and Mouth Disease (Fig. 17-21)
 - Etiology
 - ▲ Coxsackie A-16 – most common
 - ▲ Enterovirus 71 – causes CNS involvement
 - ▲ Primarily affects children age 3–10
 - Transmission (highly contagious)
 - ▲ Oral-oral
 - ▲ Oral-fecal



FIGURE 17-21 Hand, foot and mouth disease.
(Courtesy of Dr. Stephen Tying.)

- Clinical
 - ▲ Incubation period: 3 to 6 days
 - ▲ Prodrome enanthem: fever, malaise, abdominal pain
 - ▲ Oral ulcerative lesions
 - △ Location: hard palate, tongue, and buccal mucosa
 - △ 2 to 10 lesions develop over 5 to 10 days; vesicles on an erythematous base
 - ▲ Cutaneous lesions
 - △ Tender, elliptical, erythematous macules with a gray center, vesicles are surrounded by a red areola
 - △ Run parallel to skin lines
 - △ Few hundred lesions, peripherally distributed: hands, feet, and buttocks
 - △ Hands > feet

- △ Resolves spontaneously after 2–3 days without complications
- Diagnosis: isolation and identification of virus in cell culture
 - ▲ Histology:
 - △ Intraepidermal blister: neutrophils, monocytes, necrotic roof
 - △ Intercellular edema (reticular edema/balloon degeneration)
 - △ Edematous dermis
 - △ Intracytoplasmic particles in a crystalline array
 - ▲ Cell culture
 - △ Detection of Enterovirus RNA via PCR of blood, stool, and pharyngeal vesicles
 - △ Stool is least specific because children are able to excrete Enterovirus for up to eight weeks in feces from a previous infection
- Treatment: symptomatic
- Herpangina
 - Transmission: fecal-oral route
 - Etiology
 - ▲ Coxsackieviruses A 1–10, 16, or 22
 - Clinical manifestations
 - ▲ Incubation period typically is 7 to 14 days
 - ▲ Mucous membrane lesions
 - ▲ 1–2 mm, gray/white papulovesicular lesions, with an erythematous surrounding:
 - ▲ Location: soft palate tonsillar pillars, faucets, uvula
 - ▲ Sudden onset of fever, headache, sore throat, back/extremity pain
 - ▲ Exanthem: not distinctive in appearance for clinical diagnosis
 - Treatment – self limited

HEPATOVIROS

- Hepatitis A
 - Transmission: fecal – oral route
 - Affects children and adults—commonly seen in daycare, schools, and restaurants
 - Pathogenesis
 - Viral replication within the hepatocyte's cytoplasm causes a non-cytopathic infection
 - CD 8+ T lymphocytes and natural killer cells that are HAV specific assist in destruction of the infected hepatocytes leading to hepatocellular injury
 - As a result, the host's immune system ultimately causes damage to the liver
 - Clinical manifestations
 - Incubation period: 2 to 7 weeks
 - Children – acute infection is self limited

- ▲ Symptoms include: fever, malaise, vomiting, diarrhea, abdominal pain, mild hepatomegaly
- ▲ Jaundice is seen via serological detection one week after onset
- ▲ During prodrome period there is an elevation of aminotransferase levels
- Adults – symptomatic for several weeks up to six months
 - ▲ 80% present with hepatomegaly
 - ▲ 70% present with jaundice
 - ▲ Less than one percent progress to fulminant hepatic failure, often in patients with underlying liver disease
 - ▲ 11% of cases manifest as a transient, discrete, maculopapular, urticarial, or petechial rash
 - ▲ Rarely, persistent hepatitis A develops into a globulinemia with cutaneous vasculitis
- Diagnosis
 - HAV RNA detection of stool, body fluids, and liver tissue
 - **GOLD STANDARD** for acute disease: serum IgM anti HAV; the antibody is positive at onset of symptoms, peaks during the convalescent phase, and stays detectable for up to six months after
- Treatment: mild self limited disease
 - Prophylactic treatment: hepatitis A vaccine now recommended for
 - ▲ All kids 12–23 months of age
 - ▲ All international travelers
 - ▲ Patients with chronic liver disease
 - ▲ Patients with clotting factor disorders
 - Combination vaccine for the prevention of hepatitis A and hepatitis B virus has been approved

Paramyxovirus

- Spherical
- Enveloped virus
- ssRNA

RUBEOLA/MEASLES

- Most contagious virus known
- Responsible for almost 1 million deaths worldwide
- Clinical syndromes divided into three categories:
 - Typical
 - Modified—partially immune host, clinical signs are milder with longer incubation period
 - Atypical – infection of host previously immunized with killed virus vaccine
- Suspected case of rubeola is reportable by law for outbreak prevention
- Clinical manifestations
 - Incubation
 - Initiated with viral entry via conjunctivae or respiratory mucosa
 - Initial viremia—local replication and dissemination through lymphatic system and reticulo-endothelial system
 - Experience brief respiratory symptoms, or morbilliform rash, many are asymptomatic
 - Length—10–14 days
 - Prodrome
 - Second viremia occurs several days post-incubation period
 - Three Cs of measles: cough, coryza, and conjunctivitis
 - Low grade fever (101° F), malaise, anorexia
 - Length: 2–8 days
 - Enanthem: pathognomonic
 - ▲ Koplik spots – described as “grains of salt on a red background”
 - △ 1–3 mm white, gray, bluish elevations with erythematous base located on buccal and labial mucosa, adjacent to the molars
 - ▲ Appear 24 hours before exanthem
 - Exanthem
 - Non-pruritic, erythematous maculopapular rash with cephalocaudal progression
 - Rash begins post auricular, progresses across face, down the trunk as upper rash fades
 - Rarely involves palms and soles
 - Erupts 5 days post-prodrome, improvement of symptoms within two days of onset
 - Length: within 5 days, rash fades becoming non-blanching, copper-colored, followed by a fine desquamation
 - Measles is highly contagious from 4 days pre-exanthem until 4 days post-exanthem
- Complications—greater than 3 days post exanthema indicates a complication
 - Thrombocytopenic purpura
 - Tracheobronchitis – with involvement of upper respiratory tract
 - Otitis media and pneumonia from the secondary bacterial infection,
 - Reactivation of tuberculosis—secondary to effect on cellular immunity
 - Neurological syndromes
 - Subacute sclerosing panencephalitis (SSPE) – progressive degenerative disease of the CNS
 - ▲ Presents 7–10 years post infection
 - ▲ Risk factor (50%): development of measles before age 2
 - Post-infectious encephalomyelitis – autoimmune related demyelinating disease that appears within weeks of exanthem

- ▲ Symptoms: fever, headache, seizures, confusion, coma
 - ▲ CSF analysis: pleocytosis, high protein level
- Diagnosis
 - Viral isolation in tissue culture
 - Serology
 - Standard test for confirmation: serum IgM
 - Anti—measles IgM detectable three days after appearance of rash, undetectable > 30 days post exanthem
 - Hemagglutination inhibiting antibodies- ELISA used to find antibodies from blood sample on filter paper
- Histology
 - Giant cell inclusions seen in nasopharyngeal, conjunctival, and buccal epithelial cells
 - Multinucleated giant cells
 - Warthin-Finkeldey cells – giant cells with numerous overlapping nuclei located in lymphoid tissue during prodromal stage
 - Epithelial syncytial giant cells of skin and respiratory mucosa
- Treatment
 - No antiviral agent available—recent studies show susceptibility of virus in vitro to Ribavirin
 - 2nd line treatment: vitamin A (100,000–200,000 IU by mouth once daily for 2 days)
 - Isolation until 4 days after exanthem onset
- Vaccine: protective titers can last greater than 16 years
 - Post—exposure prophylaxis-non immunized infants can be vaccinated within 72 hours of exposure for protection against contraction of virus
 - Passive immunization—Immune serum globulin – given to susceptible population to prevent or modify illness if given within 6 days of exposure
 - Intramuscular injection-Dose: 0.25 mL/kg –15 mL kg (max)
 - Live vaccine is contraindicated in pregnant women
 - Anaphylactic reactions have been reported in patients with egg allergy

Togaviruses

- Enveloped
- ssRNA
 - Rubella: German measles (Fig. 17-22)
 - Affects adult and children, predominant age of infection: children 5–9 years old
 - Known as “3-day measles”
 - Pathogenesis
 - ▲ Virus acquired via inhalation of droplets and infection of nasopharyngeal cells



FIGURE 17-22 Rubella. (Courtesy of Dr. Stephen Tying.)

- ▲ Replication occurs in the cytoplasm of host cells of the nasopharynx and lymph nodes
 - ▲ Hematogenous spread leads to infection of the skin and other organs. The virus is able to freely cross the placenta
 - ▲ Host sheds the virus almost two weeks prior to the onset of the rash, and to a lesser degree, up to a week after onset of symptoms
- Incubation period: 2–3 weeks
- Transmission: via droplets or direct contact with nasal secretions
- Postnatal acquired rubella syndrome
 - Clinical manifestations
 - ▲ 25–50% of patients can be asymptomatic, symptoms are commonly more severe in adults than children
 - ▲ Generalized tender lymphadenopathy for up to a week: involves all nodes, most striking in the suboccipital, postauricular, and posterior cervical nodes
 - ▲ Low-grade fever and malaise lasting 1–2 days, begins two weeks after initial infection
 - ▲ Enanthem – “Forscheimer’s spots”

- △ Nonspecific pinpoint red macules and petechiae over the soft palate and uvula just before or along with the exanthem
- ▲ Exanthem – erythematous maculopapular rash, progresses cephalocaudally, and may be followed by desquamation, lasts 3–5 days (same distribution and appearance of measles rash, with milder symptoms)
- ▲ Myalgias and polyarthritis coincide with appearance of exanthem and can persist for a few weeks up to a month. It is most commonly found in young women
- Complications
 - ▲ Post infectious encephalitis
 - ▲ Thrombocytopenic purpura
 - ▲ Arthritis/arthritis
- Congenital rubella syndrome
 - Affects the fetus of a pregnant woman without immunity to the virus
 - Greatest hazard if fetus infected during first trimester, up to eighty percent suffer complications
- Clinical manifestations
 - Most frequent complication if infection occurs between 2–8 weeks gestation
 - Ophthalmologic: permanent cataracts, microphthalmia, and retinopathy
 - Cardiac abnormalities: patent ductus arteriosus, pulmonary stenosis, atrial and ventricular septal defects
 - Most common complication if infection occurs up to 16 weeks gestation
 - ▲ Intrauterine growth retardation
 - ▲ Sensorineural deafness
 - ▲ Neurologic: meningoencephalitis, mental retardation with behavioral disorders, large anterior fontanelle
 - ▲ Cutaneous: “blueberry muffin” purpuric skin lesion, purpura and petechiae secondary to thrombocytopenia
 - ▲ Systemic dermal extramedullary hematopoiesis
- Complications
 - Spontaneous abortion (20%), stillbirth
 - Premature delivery
 - Panencephalitis
 - Developmental endocrine abnormalities during adolescent period: hypothyroidism, diabetes mellitus, thyrotoxicosis
- Diagnosis
 - Most common method–commercial enzyme immunoassay (EIA) detection of rubella specific IgM. IgM detected 4 days after onset of rash to 8 weeks afterward

- Viral culture from nose, pharynx, blood, and urine
- Salivary antibodies to rubella
- IgG antibody to rubella virus in urine of children (up to 99% specific and sensitive)
- Fourfold increase of rubella antibody in patient serum
- Reverse transcriptase PCR detection of viral RNA prenatally, in amniotic fluid if fetus greater than 15 weeks gestation
- Treatment
 - Congenital rubella syndrome: no treatment available, acetaminophen for fever, and supportive care
 - Postnatal rubella: no specific treatment, disease is usually self-limited
 - Contact isolation in patients for 7 days after exanthem onset
 - Contact isolation necessary for congenitally infected children for one year until cultures are negative
- Preventative measures
 - MMR vaccine given in 2 doses
 - ▲ Dose #1 between 12 and 15 months of age
 - ▲ Dose #2 recommended at 4 to 6 years of age
 - Contraindicated in pregnant women
 - Relative contraindication in patients allergic to eggs, the immunodeficient or immunocompromised population
 - Most effective prevention of congenital rubella syndrome is immunization of non-immune women before pregnancy or immunization immediately post-partum

Flaviviruses

- Enveloped
- ssRNA
- Flaviviruses of clinical importance: hepatitis C, yellow fever, Dengue fever, West Nile virus

HEPATITIS C (HCV)

- Uses an RNA dependent RNA polymerase for viral replication which lacks proofreading ability and creates slightly mutated strands, leading to the difficulty in control of and development of a vaccine against the virus
- Transmission: percutaneous, body piercing and tattoos, inhaled cocaine, blood, sexual intercourse
- Population at risk: IV drug abusers, sexually active patients, health care workers, hemodialysis patients, blood transfusion recipients (especially before 1992)
- Incubation: 7–8 weeks
- Acute hepatitis C is self limited and rarely causes hepatic failure
 - 80% of cases persist greater than 6 months leading to chronic infection

- Chronic viral hepatitis is most commonly caused by HCV
 - Most patients with chronic HCV have chronic liver disease, which can progress to cirrhosis and hepatocellular carcinoma
 - Alcohol increases the clinical severity of chronic disease
- Diseases associated with chronic hepatitis C:
 - Immune complexes: skin, kidney (glomerulonephritis)
 - Sialadenitis
 - Autoimmune thrombocytopenic purpura
 - Lymphoma: increased antibodies to HCV in patients with non-Hodgkin's B-cell lymphoma (20% to 40%)
 - Mixed cryoglobulinemia (types II and III)
 - Porphyria cutanea tarda
 - Lichen planus
 - Polyarteritis nodosa (5%)
 - Pruritus (39%)
- Clinical course
 - Usually mild with no outward signs of infection
 - Symptoms indistinguishable from other types of acute viral hepatitis
 - Fever (60%), fatigue, malaise (67%), nausea and vomiting, anorexia
 - Jaundice (< 25%)
 - Hepatomegaly
 - Dark urine (84%)
 - mild right upper quadrant pain
 - Extrahepatic manifestation of HCV infection
 - Palmar erythema, spider nevi, asterix, clubbing
 - Icteric sclera, temporal muscle wasting, enlarged parotid
 - Gynecomastia, scant body hair
 - Peri-umbilical hernia, ascites, caput medusae, abdominal bruit
 - Ankle edema
- Diagnosis
 - Bilirubin – unconjugated and conjugated can be markedly elevated
 - Alkaline phosphatase – mild elevation
 - Aminotransferases – elevated 6–12 weeks post exposure in acute HCV
 - Elevation of ALT levels for 6 months or greater define chronic hepatitis
 - These levels fluctuate so a normal value does not indicate eradication of disease
 - AST/ALT ratio > 1 is associated with cirrhosis in chronic HCV
 - HCV RNA becomes positive in acute cases within eight weeks post-exposure, confirmation of ongoing diseases are established via these markers
 - Hepatitis C antibody test (anti HCV serological screening) via enzyme immunoassay test (EIA), unable to distinguish acute from chronic infection
 - Recombinant immunoblot assay – detection of antibody against 2 + antigen
 - ▲ Resolution of HCV infection is indicated by a positive immunoblot assay and two or more instances of undetectable HCV RNA
 - Quantitative assay to confirm HCV RNA, via PCR of the blood
 - ▲ This can help predict host response to treatment, and changes in HCV RNA levels
 - Positive results of EIA, RIBA, and PCR testing are diagnostic for active HCV infection, host should then be treated
 - If these markers persist for greater than six months, the disease is defined as chronic liver disease
 - Positive alpha fetoprotein in patients with chronic HCV may indicate hepatocellular carcinoma
- Histological findings
 - Lymphocytic infiltration, moderate degrees of inflammation and necrosis, and portal or bridging fibrosis are noted
 - Regenerative nodules are seen in patients with cirrhosis
- Treatment
 - Eradication of HCV is defined as absence of HCV RNA in serum for six months or greater secondary to antiviral therapy
 - Antiviral therapy should be considered if:
 - Elevated ALT levels; however up to 30% of patients with chronic HCV have normal ALT
 - Positive HCV antibody and serum HCV RNA
 - Liver biopsy shows portal or bridging fibrosis with moderate inflammation and necrosis
 - Acute HCV treatment
 - Interferon monotherapy
 - Pegylated interferon
 - Pegylated interferon + ribavirin (most effective) antiviral therapy is highly effective if given for 12–24 weeks
 - Chronic HCV treatment
 - Pegylated interferon + ribavirin. Weekly injections of PEG-IFN alfa combined with twice daily doses of ribavirin (most effective). Two types of pegylated interferon use
 - ▲ Peg-IFN alfa 2b 1.5 mcg/kg SC weekly or
 - ▲ Peg-IFN alfa 2a 180 mcg SC weekly
 - Ribavirin: 400–600 mg taken by mouth twice daily
 - Combination therapy: Treatment individualized via genotype

- ▲ HCV Genotype 1—high dose medication for 48 weeks
- ▲ HCV Genotype 2 or 3—medication given for 24 weeks
 - △ Pegylated interferon monotherapy
 - △ Interferon monotherapy
- Combination therapy is most effective against genotype 2 and 3, leads to 80% eradication of HCV RNA
 - Treatment has a better outcome in patients < 40 years old, absence of cirrhosis, and shorter duration of infection
 - Treatment precaution
- Interferon therapy aggravates autoimmune disorders, and is contraindicated in patients with platelet levels < 50,000
- Interferon therapy poses increased risk of depression and suicidal ideation and should be used with caution in certain patient populations
- Use of corticosteroids has been linked with increased mortality
- Ribavirin can induce hemolytic anemia and has strong association with birth defects and should be avoided during pregnancy

Retroviruses

- Enveloped
- ssRNA
- Use a reverse transcriptase

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

- Estimated 1.1 million people in US infected with HIV, affecting predominately young adults between ages 25–44 years
- Targets and destroys CD4 + T lymphocytes leaving the body in state of severe immunodeficiency open for opportunistic infections and malignancies
- Viral structure
 - Diploid genome – 2 molecules of RNA, p24 nucleocapsid core protein, envelope proteins: gp41 and gp120; reverse transcriptase
- Route of infection
 - HIV enters CD4 lymphocytes via adherence of envelope proteins to the cell. Reverse transcriptase converts single stranded viral RNA to double stranded DNA which is inserted into the hosts DNA. Virions are released and the lymphocytes are destroyed, eventually leading to an immunodeficient state
- HIV can infect: CD4 + T cells, macrophages, thymic cells, astrocytes and dendritic cells
- Stages of HIV infection
 - Viral transmission
 - Sexual activity (70%)
 - Coexistence of a sexually transmitted disease with genital ulceration has four times higher rate of transmission
 - Increased risk in homosexual population
- Blood and body fluids
 - Needles
 - ▲ IV drug abusers
 - ▲ Accidental needle sticks
 - Perinatal transmission in HIV infected women
 - ▲ Transmission has been reduced with HIV testing of pregnant women and treatment with antiretroviral drugs
 - ▲ Breastfeeding post-partum
 - Recipients of blood transfusions (especially between 1975–85)
 - Organ transplantation
 - Genetics
 - ▲ Patients with a homozygous CCR5 gene mutation for a cell surface protein and co receptor of the virus are immune to the HIV virus. Those with a heterozygous gene mutation have a slower course of disease. Patients with a CXCR1 gene mutation have a rapid progression of HIV to AIDS
- Primary HIV infection
 - Predominant percentage of HIV infections transmitted during this time because of increased level of viremia and very nonspecific symptoms
 - Presence of acute symptoms for greater than 14 days correlates with increased risk of progression to AIDS in 3 years
 - 6 months post infection—CD8 T cells allow viremia to level out and prevent further destruction of CD4 count
- Seroconversion
 - After 4–10 weeks post exposure, patient will have positive HIV serology
 - 95% of patients seroconvert within 6 months
 - Mononucleosis like symptoms:
 - ▲ Headache, retro-orbital pain, muscle aches, fever, pharyngitis, fatigue, lymphadenopathy, weight loss, night sweats, fine morbilliform rash and mucutaneous ulcers
- Clinical latent period
 - Period of time with no signs of virus except lymphadenopathy
 - From seroconversion to six months after transmission
 - During this time there is an increased rate of viral replication and CD4 cell destruction
 - Viral load – measures rate of disease progression and antiviral therapy response in early stage of disease. Stable at 6 months, can increase very slowly without treatment

- Early symptomatic HIV infection
 - These diseases are most severe in association with the HIV infection. Cutaneous manifestations include:
 - ▲ Thrush
 - ▲ Oral hairy leukoplakia
 - ▲ Herpes zoster (2 + episodes)
 - ▲ Bacillary angiomatosis
- AIDS
 - Defined as a CD4 + count of $< 200 \text{ cell/mm}^3$
 - ▲ CD4 + count measures degree of immunosuppression
 - Also defined by diseases which have their onset in the setting of severe immunosuppression
 - ▲ *Pneumocystis carinii* pneumonia
 - ▲ Candidiasis of the upper respiratory system
 - ▲ Kaposi's sarcoma
 - ▲ Mycobacterium avium
 - ▲ Disseminated mycobacterium tuberculosis
 - ▲ Cytomegalovirus
 - ▲ Dementia secondary to HIV infection
 - ▲ Invasive cervical anal cancer
 - ▲ Toxoplasmosis of internal organ
 - ▲ Burkitt's lymphoma
- Advanced HIV with $\text{CD4} < 50 \text{ cell/mm}^3$. Patients will survive only 1 year without antiviral therapy once their disease has become so advanced
- Clinical manifestations
 - Acute retroviral syndrome—presents four weeks after patient infected with the virus (70% of HIV + patients)
 - Primary symptoms (resembles symptoms of mononucleosis)
 - Headache, retro-orbital pain, muscle aches, fever, pharyngitis, fatigue, lymphadenopathy, weight loss, and a fine morbilliform rash, mucutaneous ulcers
- Diagnosis
 - ELISA – detects antibodies in blood to virus, 3–7 weeks after infection [high sensitivity, moderate specificity]
 - Western blot assay – confirmatory test (low sensitivity, high specificity)
 - Viral load measured by PCR
 - Baseline testing: CD4 + cell count, chest x-ray, PPD, VDRL/RPR, serology for CMV, VZV, hepatitis, and toxoplasmosis; HIV antibody test, and HIV viral load
 - Acute HIV infection diagnosed with:
 - Positive p24 antigen
 - High viral load ($> 100,000$)
 - Negative serology test
 - Mild clinical symptoms
- Antiretroviral therapy (Table 17-4)
 - Without antiviral therapy patient progresses into a stage of acquired immunodeficiency within ten years of transmission, when CD4 count reaches $< 200 \text{ cells/mm}^3$
 - Since development and use of highly active antiretroviral therapy (HAART), there has been a decline in the trend of newly infected HIV and AIDS patients
 - Treatment should be initiated if
 - Patient diagnosed with AIDS or has symptomatic HIV
 - CD4 count is below 350 cells/mm^3 ,
 - HIV RNA levels are greater than $50,000 \text{ copies/mL}$
 - Combination regimen
 - A non-nucleoside reverse transcriptase inhibitor + 2 nucleoside reverse transcriptase inhibitors

Table 17-4 Seven Classes of Antiretroviral Drugs

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Drug	Dose	Side Effects
Zidovudine [Retrovir]	200 mg three times daily	Bone marrow suppression Myopathy
Lamivudine, 3TC [Epivir]	150 mg twice daily	Hepatitis B exacerbation Hepatomegaly with steatosis Peripheral neuropathy Rhabdomyolysis Anaphylaxis Myalgia/arthralgia Abnormal dreams

(Continued)

TABLE 17-4 (Continued)

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Drug	Dose	Side Effects
Stavudine [Zerit]	40 mg tablet twice daily	Discontinue if peripheral neuropathy occurs Hyperlactatemia Severe motor weakness Leukopenia Hepatomegaly Pancreatitis Thrombocytopenia
Didanosine [Videx]	100 mg 2 tablets twice daily	Fatal and nonfatal pancreatitis Peripheral neuropathy Lactic acidosis Anaphylactoid reactions Rhabdomyolysis Hepatotoxicity Hyperlactatemia Optic neuritis
Zalcitabine [Hivid]	Discontinued in America	
Abacavir [Ziagen]	300 mg twice daily	Fatal anaphylaxis Liver failure Renal failure Adult respiratory distress syndrome Respiratory failure Severe hypotension
Emtricitabine, FTC [Emtriva]	200 mg tablet once daily	* Caution to hepatitis B patients: use can cause fatty liver Lactic acidosis Severe hepatomegaly Palmar-plantar hyper pigmentation Dyspepsia Paresthesias
Combivir	Zidovudine 300 mg Abacavir 300 mg twice daily	Zidovudine associated hematologic toxicity and myopathy Neutropenia Myositis Rhabdomyolysis Severe anemia Lactic acidosis Severe hepatomegaly Post treatment hepatitis B exacerbation
Trizivir	Zidovudine 300mg Lamivudine 150mg Abacavir 300 mg Twice daily Has good viral suppression, should be used in cases when Efavirenz is ineffective	Not for use if weight < 40 kg Fatal anaphylaxis Liver failure Renal failure Severe hypotension Adult respiratory distress syndrome Respiratory failure Lactic acidosis Rhabdomyolysis Erythema multiforme Toxic epidermal necrolysis

(Continued)

TABLE 17-4 (Continued)

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Drug	Dose	Side Effects
Atripla	Efavirenz 600 mg Emtricitabine 200 mg Tenofovir 300 mg One tablet at night on empty stomach	Associated with dizziness, drowsiness, impaired concentration Not recommended for patients younger than 18 yrs old. Sudden discontinuation of drug can severely exacerbate HBV infection
Epzicom	Abacavir 600 mg Lamivudine 300 mg Once daily	Lactic acidosis FDA pregnancy category C Increased thirst, urination Seizures, mood changes Do not take if hypersensitivity to Abacavir
Truvada	Emtricitabine 200 mg Tenofovir 300 mg Once daily on an empty stomach	Pancreatitis Lactic acidosis Severe hepatomegaly with steatosis

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) Commonly Seen Side Effects: Cytochrome P450 Inducers, Rash		
Drug	Dose	Side Effects
Nevirapine [Viramune]	200 mg daily X 14 days	Hepatotoxicity in women with reduced T-cell levels Fatal hypersensitivity reaction Steven-Johnson syndrome Rhabdomyolysis Granulocytopenia Angioedema Severe stomatitis
Delaviridine [Rescriptor]	200 mg three times daily in 3 oz water	Mild rash resolves in 3–14 days Angioedema Granulocytosis, leukopenia, pancytopenia GI bleed Cardiomyopathy Rhabdomyolysis Acute renal failure
Etravirine TMC-125 [Interlece]	100 mg 2 tablets twice daily after meals	Used for multi-resistant strains, do not use in naïve patients or children Tablet must be swallowed whole with liquids Severe skin rash, extremity tingling, high blood pressure
Efavirenz [Sustiva]	600 mg at bedtime on empty stomach	CNS symptoms: confusion, depression, hallucinations, seizures, memory loss, suicidal thoughts Exfoliative dermatitis False positive marijuana drug testing Contraindicated in pregnancy

Protease Inhibitors

Commonly Seen Side Effects: GI Intolerance, Cytochrome P450 Inhibitors, Metabolic Syndrome, Insulin Resistance, Truncal Obesity, and Hyperlipidemia

Drug	Dose	Side Effects
Saquinavir [Invirase]	500 mg 2 tablets twice daily with food Given with Norvir 100 mg once daily	Hepatotoxicity Diabetes mellitus Pancreatitis Seizures Steven-Johnson syndrome Thrombocytopenia Portal hypertension Thrombophlebitis Intestinal obstruction
Ritonavir [Norvir]	300 mg 2 tablets twice daily	If taken in combination with non-sedating antihistamines, sedatives hypnotics, anti-arrhythmics, or ergot alkaloids – has life threatening side effects.
Indinavir [Crixivan]	400 mg Two tablets every 8 hours without food	Nephrolithiasis Lipodystrophy Anemia
Nelfinavir [Viracept]	750 mg three times daily with food	Avoid mixing with acidic food/juice Diarrhea Leukopenia Suicidal ideation Hepatitis Jaundice Don't treat pregnant patients due to ethyl methanesulfonate
Amprenavir [Agenerase]	Discontinued in the United States	
Kaletra	200 mg Lopinavir + 50 mg Ritonavir Two tablets twice daily (used in pediatric and naïve population)	Pancreatitis Neutropenia Thrombocytopenia (peds) Exfoliative dermatitis Hemarthrosis in hemophiliacs
Fosamprenavir [Lexiva]	700 mg Two tablets twice daily without food – for naïve patients 700 mg Fosamprenavir two tablets/daily + 100 Ritonavir once daily without food – for resistant patients	Increased liver enzymes Severe skin reactions Neutropenia Fat redistribution Hemolytic anemia
Tipranavir [Aptivus]	250 mg co-administered with 100 mg Ritonavir Two tablets, twice daily with food	Hypercholesterolemia, hyperlipidemia Intracranial hemorrhaging Platelet aggregation and coagulation, rash Contraindicated in: treatment naïve patients, potent CYP 3A inducers, Child-Pugh class B or C

(Continued)

Protease Inhibitors		
Drug	Dose	Side Effects
Darunavir [Prezista]	Prezista 300 mg 2 tables twice daily with food Taken with Ritonavir 100 mg 1 tablet twice daily with food for resistant patients ** Must be taken with Ritonavir to keep Prezista level high in blood	Severe skin rashes Neutropenia Fat redistribution Inflammation nose and throat **Contains sulfa Avoid if hepatic impairment
Atazanavir [Reyataz]	200 mg Two tablets once daily with food (naïve patients) 300 mg Atazanavir + 100 mg Ritonavir One daily with food – resistant patients	1st or 2nd degree AV block PR prolongation Severe hyperglycemia Neutropenia Erythema multiforme Dysuria, hematuria Jaundice Immune reconstruction syndrome Elevated CK

Nucleotide Reverse Transcriptase Inhibitors		
Drug	Dose	Side Effects
Tenofovir [Viread]	300 mg daily	Lactic acidosis Severe hepatomegaly Nephrotoxicity Hypophosphatemia Fanconi syndrome Acute renal tubular necrosis Osteomalacia with renal tubulopathy Dyspnea

Fusion Inhibitors		
Drug	Dose	Side Effects
Enfuvirtide, T-20 [Fuzeon]	90 mg subcutaneous injection twice daily for resistant strains	Injection site reactions: redness, swelling, itching Increased risk of bacterial pneumonia Glomerulonephritis Guillain-Barré syndrome

CCR5 Co-receptor Antagonist

Drug	Dose	Side Effects
Maraviroc [Selzentry]	300 mg twice daily ** only effective against CCR5-tropic HIV	Myocardial ischemia or infarction Orthostatic hypotension Hepatotoxicity Infection Malignancy

Integrase inhibitor
To Be Used in Combination With Other Antiretroviral Medications

Drug	Dose	Side effects
Raltegravir [Isentress]	400 mg twice daily Used in multi-drug resistant strains	Diarrhea, nausea, headache Skin rash Myopathy Rhabdomyolysis Elevated levels of creatinine kinase Gastritis Myocardial infarction

- Protease inhibitor + 2 nucleoside reverse transcriptase inhibitors
- 3 nucleoside reverse transcriptase inhibitors (least effective)
- Goal: to reduce viral load, and increase CD4 counts

- A. HBsAG
- B. HBcAG
- C. HBsAb
- D. HBeAg
- E. HAAG

QUIZ

Questions

1. A 28-year-old pregnant (2 months) woman from Iran has an erythematous rash that started on the head and spreads to the trunk. She has had three days of fever associated with pain in the back of her neck, joint pain, and headache. The probability that the baby will be infected is:
 - A. 85% to 90%
 - B. 100%
 - C. The baby will not be infected
 - D. 10%
 - E. 40% to 60%
2. Which of the following serologic markers is the most important to determine newborn infection with hepatitis B?
 - A. HBsAG
 - B. HBcAG
 - C. HBsAb
 - D. HBeAg
 - E. HAAG
3. A college student does not go to her scheduled class. She has fever, sore throat, malaise, fatigue and a bump in the right side of the neck. Her abdominal exam showed an increased liver size. The microscopic exam of the epithelial cells revealed a giant nuclei surrounded by clear zones. The cause of the infection is:
 - A. Cytomegalovirus
 - B. HIV
 - C. Herpes virus type 1
 - D. Herpes virus type 2
 - E. Papilloma virus
4. A 3-year-old infant is taken by his mother to the doctor. She says he has had fever, malaise and abdominal pain for the last 4 days, today he presents with erythematous macules with a gray center and vesicles surrounded by erythema. The lesions are distributed on hands, feet and buttocks. The infectious virus is:

- A. ssRNA enveloped virus
 - B. dsRNA non enveloped virus
 - C. ssRNA nonenveloped virus
 - D. dsDNA noneveloped virus
 - E. dsDNA enveloped virus
5. A pregnant woman has small (1 to 3 mm), discrete, smooth-surfaced, flesh-colored papules. Some may coalesce into larger plaques. The lesions started 2 months ago, and they have been increasing in size and number. She visits her doctor and asks for treatment. Which of the following options would be the best for her?
- A. Podophyllin
 - B. Podophyllotoxin
 - C. 5-Fluorouracil
 - D. Imiquimod
 - E. Cryotherapy
6. A 6-year-old girl presents with a rash that started on the trunk and spread to the face and extremities. At physical exam she presented with vesicles, pustules and crusts on her skin. Her mother had the infection 5 years ago and she had a new baby 1 month ago. Which immunoglobulin will protect the 1-month-old baby from getting the infection?
- A. IgM
 - B. IgG
 - C. IgE
 - D. IgD
 - E. IgA
7. A 12-year-old boy is brought in by his mother with the complaint of a rash that began 4 days ago. She states she believed her son had the flu about a week before the rash onset. He suffered from cough, runny nose, watery eyes, and was very lethargic. She treated him with over-the-counter decongestants and children's Tylenol for his fever, which she said reached 101 degrees Fahrenheit. Just 3 days ago she noticed a non-pruritic erythematous rash had appeared behind his ears, and now had spread down to his trunk and upper extremity. Physical examination of the patient reveals an erythematous maculopapular rash across his face and on the anterior aspect of his trunk. Two-mm blue-gray papules with erythematous base are visualized adjacent to his lower molars. The patient appears alert and oriented to time and place, and is able to follow the commands of the doctor. The papules visualized adjacent to his molars are commonly known as:
- A. Nikolsky sign
 - B. Koplik spots
 - C. Forchheimer's sign
 - D. Herpangia
 - E. Hand-foot-and mouth disease
8. An 8-year-old black male with sickle cell anemia complains for two days of malaise and his mother noticed an erythematous, lacy macular eruption on the cheeks, trunk and extremities. His doctor is concerned that this viral infection will cause an aplastic crisis. The virus related to this association is:
- A. Varicella zoster virus
 - B. Herpes simplex virus
 - C. Coxsackie A-16
 - D. Coxsackieviruses A 1-10
 - E. Parvovirus B19
9. A 16-year-old high school student presents to the nurse with complaints of problems swallowing, extreme fatigue and a pruritic erythematous rash. Physical examination of the girl shows swollen erythematous tonsils, tender and enlarged cervical lymph nodes with mild hepatosplenomegaly. The patient's mother has been administering ampicillin to the child for the past 2 days. Blood tests of this patient would reveal:
- A. Hyperlipidemia
 - B. An increase concentration of IgM antibodies to EBV
 - C. Leukopenia
 - D. Microcytic anemia
 - E. A decrease concentration of IgG antibodies to HCV
10. A 33-year-old male presents to a local clinic by his ski lodge with complaints of low grade fever, headaches, muscle aches, and a vesicular rash of the upper extremity for the past 5 days. Closer examination of the rash reveals vesicles shaped as teardrops mounted on an erythematous base intermixed with resolving crusted lesions along his trunk, face, and mucous membranes. Scrapings of the vesicles are expected to reveal:
- A. Eosinophils
 - B. Owl's eyes inclusion bodies
 - C. Hyphae
 - D. Multinucleated giant cells
 - E. None of the above

Answers

1. E. The greatest danger from rubella is to the fetus. If the infection occurs during the first 2 months of gestation the risk varies from 40% to 60%. If

- the infection occurs during the fourth month the risk to infection will drop to 10%. A and B do not represent the risk during the pregnancy period described. C. Rubella has a vertical transmission. D. 10% is the risk that the fetus will be infected if the mother gets infected during the fourth month of pregnancy.
2. D. HBsAg is an important indicator of transmissibility and virus replication. A. HBsAg is found on the surface of HBV; it is positive during acute disease. The continued presence indicates carrier stage. B. HBcAg is positive during the window phase; Ig M HBcAb is an indicator of recent disease. C. HBsAb is the antibody to HBsAg; provides the immunity to hepatitis B. E. HA Ag is the antigen for HAV.
 3. A. Cytomegalovirus produces the owl's eye nuclei (giant nuclei surrounded by clear zones). B. Epithelial cells do not show HIV. C and D. Herpes histology will show ballooning of the infected cells, intranuclear inclusions and multinucleated giant cells. E. Papilloma virus is characterized by the presence of abnormal cells that have a vacuolated with clear cytoplasm or perinuclear halos and nuclear pyknosis.
 4. C. The virus infecting this infant is a coxsackie A-16. It is a picornavirus and is an ssRNA non-enveloped virus. A. HCV is an ssRNA enveloped virus. C. HEV is an ssRNA non enveloped virus. D. HBV is a dsDNA nonenveloped virus.
 5. E. Cryotherapy is a destructive method that does not cause any harm to the fetus when it is used as therapy for genital warts. A, B and C are teratogenic drugs. D. Does not have studies that support its use in genital warts in pregnancy.
 6. B. IgG is the only immunoglobulin that diffuses into fetal circulation. It will provide protection during the first 4 to 6 months of life. A. IgM is a pentamer and is the first antibody detected in serum after exposure to an antigen. C. IgE is involved in hypersensitivity and allergic reactions. It leads to mast cell degranulation and the release of leukotrienes. D. It does not reach appreciable plasma concentrations. Functions as a cell surface receptor. E. IgA is found in tears, colostrum, saliva and other secretions.
 7. B. Koplik spots are pathognomonic for measles, which commonly affects children. They can be described as "grains of salt on a red background." The spots are 1–3mm blue-gray elevations with an erythematous base. They are often found on the buccal mucosa, adjacent to the lower molars. The Koplik spots surface about 24 hours before the rash appears on the patients face. Commonly, within 5–6 days the rash, fever and Koplik spots fade with no further complications. A. Nikolsky sign is described as the result of the loss of epithelial cell-to-cell adhesion of the skin. In patients suffering from an autoimmune skin disorder such as pemphigus, if pressure is applied to the skin an extension of the blister to the adjacent area of skin is seen. D. Herpangia manifests itself on the mucus membrane as 1–2 mm slight elevated gray-white papulovesicular lesions with an erythematous surrounding. They are often seen on the soft palate, uvula, and posterior pharynx. This disease is caused by the coxsackieviruses. E. The oral ulcerative lesions of hand-foot-mouth disease are often located on the palate, tongue, as well as the buccal mucosa. They are caused by the coxsackieviruses, and are small rapidly ulcerating lesions, and are on an erythematous base.
 8. E. Parvovirus infection is associated with aplastic crisis in sickle cell anemia patients. Varicella zoster virus is associated with encephalitis or pneumonia when its infection results in chickenpox. Herpes simplex virus is not associated with aplastic crisis but type 1 can cause Ramsay hunt. Coxsackie A-16 produces hand-foot-mouth disease. Coxsackie A-1 to -10 produce herpangina.
 9. B. This patient is suffering from infectious mononucleosis, which commonly affects patients in their late teens through their twenties. This patient presents with classic clinical symptoms such as extreme fatigue, cervical adenopathy, and hepatosplenomegaly. Since this patient is suffering from an acute disease it is expected that the patient will have an increase in IgM antibodies against Epstein-Bar virus (EBV). A, D. An elevated lipid count or a microcytic anemia is incorrect. An acute EBV infection has no affect on lipid levels or red blood cells. C. Usually with an infection it is expected that the total white blood cell count will increase by 20%, not decrease. E. This patient is suffering from acute infectious mononucleosis, not hepatitis C. You would expect to see elevated titers of IgM in an acute infection, not IgG.
 10. D. Patients suffering from herpes zoster will initially present with an erythematous maculopapular rash that rapidly evolves into a grouped vesicular rash within three to four days and resolves two weeks later. Scraping of the vesicular rash are expected to show multinucleated giant cells, when are visualized on a Tzanck smear. Eosinophils are expected to be found in scraping of erythema toxicum vesicles of the newborn. Owl eye inclusion bodies are pathognomonic for CMV infections and not expected to be seen in this patient. Hyphae are normally obtained from vesicular scrapings of children suffering from candidal diaper dermatitis.

These are commonly due to infrequent diaper change or use of antibiotics.

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BACTERIAL DISEASES

STEVEN MARCET
ASRA ALI

GRAM-POSITIVE BACTERIAL DISEASES

Impetigo (Fig. 18-1)

- Superficial nonfollicular infection most often due to *Staphylococcus aureus* or group A *Streptococcus* occurs more commonly in children
- Clinical:
 - Lesions can begin as an erythematous papules that evolves into a vesicle or pustule. The pustules may rupture leaving contagious honey-colored crusts
- Treatment: topical mupirocin
- Bullous impetigo is a toxin-mediated erythroderma (Fig. 18-2) is caused only by *Staphylococcus aureus*
- Separation of the epidermis is due to exotoxin produced by staphylococci
- Toxin cleaves desmoglein 1
- Sharply demarcated flaccid bullae without surrounding erythema
- Seen most frequently in newborns
- Treatment: dicloxacillin or first-generation cephalosporin, topical mupirocin
- Glomerulonephritis may follow up to 5% of cases of impetigo

Ecthyma

- Differs from impetigo in that the dermis is ulcerated
- Usually caused by group A beta-hemolytic streptococci
- Clinical:
 - Most commonly affects the lower extremities of children, persons with diabetes, and neglected elderly patients
 - Often occurring with lymphadenitis
 - Thick crusted ulcer that heals slowly and may produce a scar
- Histology: ulceration to dermis with bacteria, crusting and an acute inflammatory infiltrate

- Treatment: usually dicloxacillin or first-generation cephalosporin, parental antibiotics may be needed for widespread infection.

Bacterial Folliculitis (Fig. 18-3)

- Most cases caused by *S. aureus*
- Clinical:
 - Superficial infection: (facial involvement is called Bockhart's folliculitis): red papules/pustules, follicularly-centered
 - Deep infection: (facial involvement is termed sycosis barbae); erythematous, fluctuant nodules
 - Lupoid sycosis: chronic form of sycosis barbae associated with scarring
- Treatment: topical antibiotics, systemic antibiotics may be indicated

Furuncles/Carbuncles (Fig. 18-4)

- *S. aureus* most commonly found
- Clinical:
 - Deep-seated nodules around hair follicle (inflammation involves the subcutis)
 - Multiple furuncles make a carbuncle, evolve from preceding folliculitis
- Treatment: topical mupirocin and dicloxacillin; if large, then also need drainage

Abscess (Fig. 18-5)

- Cutaneous abscesses represent a collection of purulent debris in the skin
- Usually *Staphylococcus aureus* (including possibly methicillin-resistant strains)
- Inguinal and perineal area may involve gram-negative flora
- Clinical:
 - Deep-seated nodules around hair follicle (inflammation involves the subcutis)
 - Fully-formed lesions are fluctuant

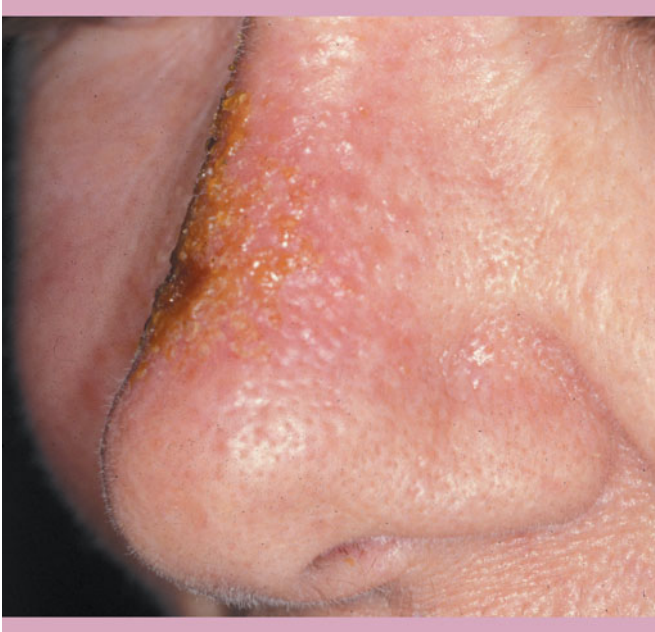


FIGURE 18-1 Impetigo. (Courtesy of Dr. Steven Mays.)



FIGURE 18-2 Bullous impetigo. (Courtesy of Dr. Steven Mays.)

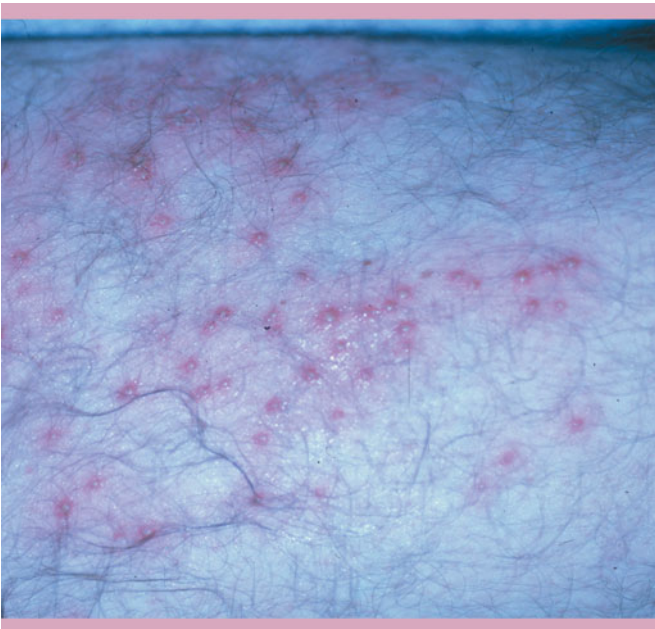


FIGURE 18-3 Folliculitis. (Courtesy of Dr. Steven Mays.)

- May be accompanied by fever, cellulitis, lymphangitis, lymphadenopathy, or leukocytosis
- Culture (useful when MRSA suspected)
- Treatment: warm compresses (to “ripen”), incision and drainage, systemic antibiotics

Lymphangitis

- Infection and inflammation of the lymphatic channels



FIGURE 18-4 Furuncle. (Courtesy of Dr. Steven Mays.)

- Variety of causal bacteria – group A *Streptococcus*, *S. aureus*, even *Pasturella multocida* (cat-scratch fever)
- Clinical
 - Erythematous and irregular appearing linear streaks in the skin

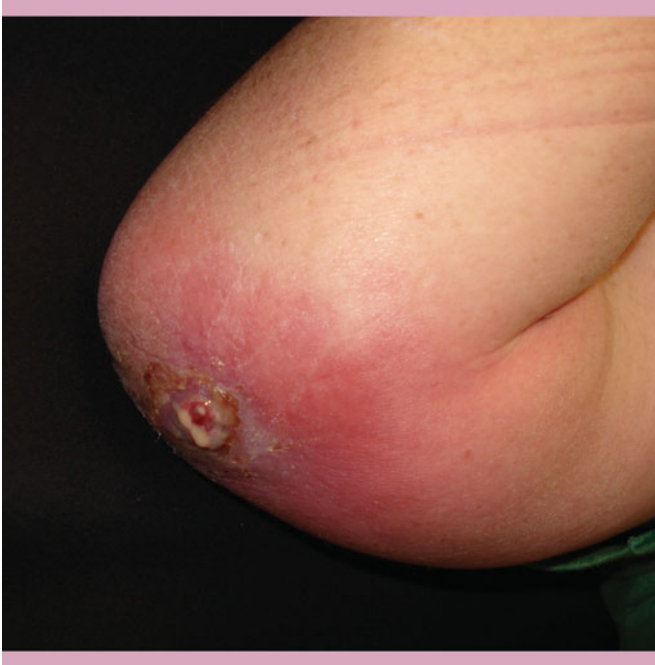


FIGURE 18-5 Abscess. (Courtesy of Dr. Asra Ali.)

- Extending from the primary infection site toward regional lymph nodes
- Streaks may tender and warm
- Can progress to bacteremia (particularly with group A strep)
- Diagnosis: complete blood count (leukocytosis), blood cultures (exclude bacteremia)
- Treatment: oral antibiotics with close follow-up, consider use of parenteral antibiotics in cases with systemic symptoms

Cellulitis

- Acute bacterial infection of skin and soft tissues
- Often follows an introduction via fissuring, laceration, puncture or insect bite
- Vast majority of cases caused by *Staph aureus*
- May rarely be caused by *Streptococcus pneumoniae* or marine vibrio species
- Clinical:
 - Characterized by expanding edema, erythema, warmth, pain, tenderness
 - The lesions are not sharply circumscribed
 - Fever is common, and lymphangitis or lymphadenopathy may accompany the disease
 - Epidermal necrosis or disproportionate pain may indicate necrotizing fasciitis
- Treatment: mild cases treated with first-generation cephalosporins or dicloxacillin, more severe cases may be hospitalized for parenteral antibiotics

Staphylococcal Scalded-Skin Syndrome (Ritter's Disease)

- Typically seen in children younger than 4 years of age
- Can occur in adult patients with renal insufficiency (cannot clear exotoxin)
- Exotoxins A or B; elaborated by bacteria, disseminated systemically
- Exotoxins cleave desmoglein 1 (similar mechanism to localized bullous impetigo); these toxins are serine proteases that actually cleave the desmoglein rather than simply binding to it.
- *S. aureus*: phage group II (types 3A, 3B, and 3C) (types 55 or 71) (exfoliative variants)
- *S. aureus* originates from a focus of infection other than the skin (differs from localized bullous impetigo)
- Clinical
 - Superficial blistering owing to disruption of the epidermal granular cell layer
 - Sparing of mucous membranes
 - Nikolsky's sign present (extension of a blister resulting from lateral pressure to the border of an intact blister)
 - Periorificial and flexural accentuation may be observed
- Diagnosis:
 - Frozen section tissue analysis to exclude toxic epidermal necrolysis (TEN) by level of blister formation:
 - SSSS – subcorneal separation
 - TEN – subepidermal separation
 - Cultures of bullae are typically negative, but cultures from other sites (oral/nasal cavities, throat, axillary/genital/umbilical regions, blood) may demonstrate staphylococcus
 - Gram's stain and/or culture from the remote infection site
- Treatment: intravenous penicillase-resistant penicillin, supportive measures
- Prognosis: mortality rate less than 4% in children, greater than 50% in immunosuppressed patients

Staphylococcal Toxic Shock Syndrome (TSS)

- Toxins produced by *S. aureus*, many that act as superantigens, lead to pro-inflammatory cytokine cascades involving tumor necrosis factor, interleukin-1, M protein, and interferon- γ
- Toxin-1 (TSST-1) causes most menstrual-related cases
- Many in the population have protective antibodies for these toxins and are not predisposed to the disease
- TSS may be associated with non-rayon tampons, surgical packings, nasal packing
- Criteria for staphylococcal toxic shock syndrome:
 - Prodromal period of 2 to 3 days

- Fever, hypotension
- Skin findings: diffuse rash, occasionally patchy and erythematous, with desquamation occurring approximately 1 to 2 weeks later
- Involvement of three or more organ systems:
 - Gastrointestinal: vomiting or diarrhea
 - Muscular: myalgia, increased creatine phosphokinase level
 - Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
 - Renal: increased blood urea nitrogen or creatinine, urinary sediment with pyuria (without evidence of urinary tract infection)
 - Hepatic: increased total bilirubin, serum glutamic-oxaloacetic transaminase (AST, SGOT), or serum glutamic-pyruvic transaminase (ALT, SGPT)
 - Hematologic: platelets $< 100,000/\text{mm}^3$
 - Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent
- Negative results on the following tests
 - Rocky Mountain spotted fever
 - Leptospirosis
 - Measles
 - hepatitis B
 - antinuclear antibody
 - false-positive Venereal Disease Research Laboratory (VDRL) test results
 - Antibodies to Monospot testing
- Treatment: penicillinase resistant penicillin, clindamycin, intravenous gamma globulin, fluid replacement

Streptococcal Toxic Shock Syndrome

- *S. pyogenes* exotoxin A (SPEA) and *S. pyogenes* exotoxin B (SPEB): produced by group A beta-hemolytic streptococci
- Criteria for streptococcal TSS:
 - Isolation of group A *Streptococcus* from a normally sterile site (e.g., blood, cerebrospinal fluid, surgical wounds) or a non-sterile site (e.g., throat)
 - Hypotension (as defined earlier)
 - Involvement of two or more organ systems:
 - Renal: increased blood urea nitrogen or creatinine
 - Hematologic: coagulopathy
 - Hepatic: increased liver enzymes
 - Respiratory: acute respiratory distress syndrome
 - Cutaneous: tissue necrosis, (i.e., necrotizing fasciitis), erythematous rash
- Desquamating rash

- Treatment: intravenous penicillinase-resistant penicillin, clindamycin, fluid therapy, and supportive measures

Blistering Distal Dactylitis

- Group A beta-hemolytic streptococci
- Clinical:
 - Tense purulent blister of distal finger or toes, volar pad
 - Common in children, more rare in adults
 - Can be confused with herpetic whitlow
- Treatment: dicloxacillin or first-generation cephalosporin

Erysipelas (Fig. 18-6)

- Group A beta-hemolytic streptococci
- Clinical:
 - Febrile illness
 - Brightly erythematous, indurated plaque, often on face or legs with sharp margins
 - Lymphedema and chronic tinea pedi may predispose
- Diagnosis: antistreptolysin (ASO) may have some utility
- Treatment: penicillin, cephalosporins or macrolides (azithromycin or erythromycin)

Scarlet Fever

- Toxin-producing group A beta-hemolytic streptococci (GABHS)



FIGURE 18-6 Erysipelas. (Reprinted with permission from Connor DH et al. *Pathology of Infectious Diseases*. Stamford, CT: Appleton & Lange; 1997, p. 819.)

- Produces erythrogenic exotoxin
- Clinical:
 - Fever and pharyngitis
 - Mucous membrane changes: white strawberry tongue turns into red strawberry tongue after 4 days
 - Skin changes: 2 to 4 days after initiation of fever, sandpaper-like rash starting on trunk then becomes more generalized; desquamates after 4 to 5 days
 - Circumoral pallor
 - Pastia's lines: linear petchial rash over skin folds (axillary/antecubital)
- Diagnosis: antistreptolysin O (ASO) titers
- Treatment: penicillin or erythromycin

Erythrasma (Fig. 18-7)

- *Corynebacterium minutissimum* a lipophilic gram-positive aerobic diphtheroid
- Clinical:
 - Superficial infection of the intertriginous areas (axillae, groin, digital web-spaces)
 - White maceration between fourth and fifth webspace
 - Inner thighs have reddish brown plaques without central clearing
- Diagnosis: fluoresce "coral red" with Wood's lamp (owing to production of coproporphyrin III by the bacteria)
- Treatment: erythromycin or benzoyl peroxide

Trichomycosis Axillaris

- *Corynebacterium tenuis* (gram-positive diphtheroid)
- Clinical:
 - White concretions on hair shaft, usually in axillae



FIGURE 18-7 Erythrasma. (Courtesy of Dr. Steven Mays.)

- Occasionally affects pubic hair (trichomycosis pubis)
- Often seen with hyperhidrosis, usually asymptomatic; however, patients may complain of malodorous sweat
- Treatment: shave affected hair; use topical clindamycin or erythromycin

Pitted Keratolysis (Fig. 18-8)

- *Kytococcus sedentarius* (previously *Micrococcus sedentarius*)
- Bacteria proliferate and produce proteinases: destroy the stratum corneum, creating shallow pits on soles
- Clinical:
 - Seen with sweaty feet
 - Malodor owing to the production of sulfur-compound by-products
- Treatment: reduce hyperhidrosis, topical clindamycin or erythromycin

Erysipeloid

- *Erysipelothrix rhusiopathiae* (gram-positive bacillus)
- Direct contact with infected meat, fish, or animal products
- Three clinical forms
 - Localized cutaneous form (erysipeloid of Rosenbach): purplish raised plaque, well demarcated on hand (common in fishermen and butchers)
 - Diffuse cutaneous form: Multiple lesions appear on various parts of the body.



FIGURE 18-8 Pitted keratolysis. (Courtesy of Dr. Ronald Rapini.)

- Generalized or systemic infection associated with endocarditis
- Treatment: penicillin, ciprofloxacin, third-generation cephalosporin

Anthrax

- *Bacillus anthracis* (gram-positive bacillus)
- Exposure to sick animals or contaminated wool, hair, or animal hides
- Two virulence factors: (1) D-glutamyl polypeptide capsule; (2) pair of toxins: edema toxin and lethal toxin
- Clinical:
 - 1- to 12-day incubation period, followed by a low-grade fever and malaise
- Pulmonary anthrax (wool sorter's syndrome):
 - Five percent of anthrax cases
 - Inhalation of anthrax spores
 - Nonspecific symptoms: low-grade fever and a nonproductive cough
 - Hemorrhagic mediastinal infection
 - Can result in septicemic anthrax
 - Chest x-ray: widened mediastinum with hemorrhagic pleural effusions
 - Usually fatal
- Gastrointestinal anthrax
 - Ingestion of infected meat products
 - Mainly affects the cecum
- Cutaneous anthrax
 - Occurs 1 to 7 days after skin exposure
 - "Malignant pustule": central area of coagulation necrosis (ulcer with eventual eschar), edema and vesicles filled with bloody or clear fluid (actually *not* pustular)
 - Ruptures to leave a black eschar and scar
 - Regional lymphadenopathy may persist
 - Most cases of simply zoonotically acquired cutaneous anthrax are not fatal (<20% fatality untreated, <1% fatality treated)
 - Anthrax meningitis may occur after bacteremic seeding from any form of anthrax
- Diagnosis:
 - Stain exudates from ulcer with methylene blue or Giemsa
 - Culture on blood agar: from skin, pleural fluid, cerebrospinal fluid (CSF)
 - Serologic diagnosis (ELISA)
 - Blood cultures
 - Skin biopsy: organisms can be seen within capillaries
- Treatment
 - Penicillin, doxycycline
 - Quinolones if patient is unable to take penicillin, doxycycline
 - Postexposure prophylaxis to prevent inhalation anthrax for 60 days

- Vaccine exists but is not readily available
- Do not incise and drain secondary to dissemination
- Considered by the CDC to be a viable weapon of bioterrorism (Category A)

Necrotizing Fasciitis (NF)

- Life-threatening soft tissue infection, needs urgent care and consultation
- Group A beta-hemolytic streptococci or caused by *Clostridium perfringens*
- Type I: polymicrobial
- Type II: group A streptococcal ("flesh-eating" strep)
- Type III: gas gangrene or clostridial myonecrosis
- Can occur as a complication of a number of surgical procedures
- Clinical
 - In early stages, pain out of proportion to physical findings
 - Begins with erythema progressing to vesiculation or bullae formation
 - Spreads from the subcutaneous tissue along the superficial and deep fascial planes
 - Ischemia and tissue necrosis due to thrombosis
 - Crepitus present with gas-forming aerobes
 - Septicemia
 - Fournier's gangrene
 - Localized variant of type I NF involving genitocrural areas (usually men but can be women)
- Diagnosis
 - Standard radiographs or computed tomography (CT) to visualize free air
 - Deep incisional biopsy will demonstrate bacteria, thrombosis and tissue necrosis
 - Culture
 - Tissue biopsy
 - Gram stain
- Treatment
 - Aerobes: (usually gram-negative organisms), ampicillin, and gentamicin
 - Anaerobes: clindamycin, or metronidazole
 - Intravenous immunoglobulin
 - Surgical debridement

Actinomycosis

- Caused by *Actinomyces israelii*, a filamentous, anaerobic, gram-positive bacteria
- Cutaneous disease includes cervicofacial disease (lumpy jaw) or cutaneous mycetoma (Madurosis)
- Clinical:
 - Cervicofacial – abscess with draining sinus, usually at the angle of the jaw or in submandibular area, sulfur granules may be seen in the exudate

- Madurosia – cutaneous pyoderma with characteristic purulent draining with discharged “sulfur granules” (aggregates of filamentous bacteria)
- Diagnosis:
 - Complete blood count: mild leukocytosis
 - Culture
 - Gram-stained smear: branched, gram-positive filamentous rods
- Treatment: penicillin, tetracyclines are alternatives; Madurosia often requires surgical intervention or even amputation

GRAM-NEGATIVE BACTERIAL DISEASES

Ecthyma Gangrenosum

- Bacteremia with skin lesions
- *Pseudomonas aeruginosa* (gram-negative rods)
- Clinical
 - Hemorrhagic bullae that develop into black eschars
 - Gluteal or perineal region (57%), extremities (30%), trunk (6%)
 - Most often in immunocompromised patients (neutropenic or those with HIV infection)
- Diagnosis:
 - Gram stain
 - Blood cultures
 - Histology: vascular necrosis with inflammatory cells and surrounding bacteria
- Treatment: penicillins, aminoglycosides, fluoroquinolones, third-generation cephalosporins, or aztreonam

Green Nail Syndrome

- *P. aeruginosa*
- Greenish discoloration in areas of onycholysis due to pigment production: —pyocyanin: blue, fluorescein: yellow/green, pyomelanin: black
- Seen in people who chronically have their hands in water
- Treatment: acetic acid solution and/or thymol 4% solution

Pseudomonas Folliculitis

- Hot tub folliculitis
- *P. aeruginosa*
- Clinical:
 - Exposure to whirlpools, swimming pools, and hot tubs
 - Pustular eruption in follicular distribution on trunk (underneath swim-wear)
- Treatment: self-limited, acetic acid soaks, quinolones in severe cases

Gram-Negative Folliculitis

- *Proteus*, *Klebsiella*, *Escherichia*, and *Serratia* spp.
- Complication in patients with acne vulgaris and rosacea who have received systemic antibiotics for prolonged periods of time
- Clinical
 - Acne that has not been responding to antimicrobial therapy or other therapy: 80% of patients
 - Patient’s acne suddenly flares: 20% of patients
 - Superficial pustular lesions without comedones
 - Deep, nodular, and cystic lesions
- Laboratory studies: Gram stain and culture
- Treatment: isotretinoin, systemic antibiotics

Malakoplakia

- Commonly due to *Escherichia coli*
- Seen mainly in immunocompromised patients
- Mainly affects genitourinary tract but may occasionally involve the skin
- Clinical
 - Yellow to pink papules, nodules, or ulcerations
 - Draining abscesses/sinuses
 - Common areas of presentation; perianal or inguinal areas, the buttocks, and the abdominal wall
- Diagnosis:
 - Histology: foamy histiocytes with basophilic inclusions containing calcium and iron - referred to as Michaelis-Gutmann bodies (stain with von Kossa for calcium and Perls Prussian blue for iron, also stain with periodic acid-Schiff and are diastase resistant); histiocytes with fine eosinophilic cytoplasmic granules (von Hansemann cells) can also be seen
 - Culture fluid from sinuses: check for bacterial (aerobic and anaerobic), fungal, and mycobacterial pathogens
- Treatment: quinolone antibiotics and sulfonamides, excise skin lesions and drain abscesses

Rhinoscleroma

- *Klebsiella rhinoscleromatis* (gram-negative coccobacillus)
- Chronic granulomatous condition of the nose and upper respiratory tract
- Inhalation of droplets or contaminated material
- Clinical
 - Three stages:
 - rhinitic: purulent rhinorrhea,
 - proliferative,
 - ▲ Affects nose most often: intranasal rubbery nodules or polyps
 - ▲ Epistaxis (bloody nose)

- ▲ Hebra nose: nasal enlargement, deformity, and destruction of the nasal cartilage
 - fibrotic: sclerosis and fibrosis with possible stenosis
- Diagnosis
 - Culture
 - CT scan: soft-tissue masses of variable sizes
- Histology
 - Mikulicz cells: parasitized histiocytes
 - Silver stains (Warthin-Starry) can be used to highlight the bacteria
 - Russel body: eosinophilic bodies inside and outside plasma cells secondary to increased IgG
- Treatment
 - Surgery combined with antibiotic therapy
 - Tetracycline, ciprofloxacin, and rifampin

Meningococcal Disease (Fig. 18-9)

- *Neisseria meningitidis* (obligate aerobic, encapsulated gram-negative diplococcus)
- Serogroups A, B, C, W135, X, Y, and Z
- Transmitted from person to person via respiratory secretions
- 20–40% of young adults are carriers of the bacteria
- Persons with deficiencies of terminal complement components C5 to C9 or properdin, immunoglobulin deficiency, asplenia, and HIV infection are most susceptible
- Direct invasion of endothelial cells and indirect damage from endotoxin release
- Clinical
 - Cutaneous findings:
 - Petechiae

- Pustules, bullae, and hemorrhagic lesions with central necrosis
 - Stellate purpura with a central gunmetal-gray hue
- Fulminant meningococemia
 - Can present as purpura fulminans
 - Waterhouse-Friderichsen syndrome: symmetric peripheral gangrene, cyanosis, hypotension, and profound shock
- Meningitis
 - Headache and a stiff neck
 - Lethargy or drowsiness
- Chronic meningococemia: one week to as long as several months with recurrent fever and variable rash usually occurring on pressure areas or around painful joints
- Diagnosis
 - Blood and throat cultures on blood agar
 - Lumbar puncture
 - Gram stain of lesional skin biopsy or aspirate specimens
 - Histology: acute vasculitis with meningococci seen in thrombi of dermal vessels
- Prevention: a new, longer-acting, conjugated vaccine exists for types A, B, C, W135, and Y that can be administered to patients 11 to 55 years of age
- Treatment: penicillin G, third-generation cephalosporin

Bartonella Species

- Cat-scratch disease, oryza fever, verruga peruana, bacillary angiomatosis, trench fever
- Aerobic gram-negative organisms

CAT-SCRATCH DISEASE (BENIGN LYMPHORETICULOSIS)

- Mainly caused by *Bartonella henselae* (gram-negative bacillus)
- Vector: cat flea (*Ctenocephalides felis*): maintains infection in cats
- Clinical
 - Infection spread by bite or scratch from cats (particularly kittens), incubation of 3–12 days
 - Fever in 25% to 75% of patients
 - Constitutional symptoms: anorexia, myalgias
 - Red papules appear at the site of scratch (develops over 3 to 10 days)
 - Lymphadenopathy (develops 1 week to 2 months after exposure)
 - Fifty percent have involvement of a single node
 - May last 6 weeks to 2 years
 - Parinaud oculoglandular syndrome: unilateral conjunctivitis and regional lymphadenitis
 - CNS changes 1 to 2%: headaches, mental status changes, seizures, encephalitis, cerebrospinal fluid usually normal



FIGURE 18-9 Meningococcal disease. (Courtesy of Dr. Asra Ali.)

- Diagnosis:
 - Indirect fluorescent antibody (IFA) for *Bartonella* (cross-reactivity between *B. henselae* and *B. quintana*)
 - Brown-Hopp tissue Gram stain and Warthin-Starry silver staining show small, curved, gram-negative bacilli
 - Fourfold rise in IgG antibody levels
 - Lymph node biopsy: necrotizing granulomas
- Treatment
 - Immunosuppressed patients: azithromycin, erythromycin, doxycycline, septrin, rifampin, ciprofloxacin, gentamycin
 - Immunocompetent patients: supportive care since CSD is a self-limiting disease

BACILLARY ANGIOMATOSIS (FIG. 18-10)

- Etiologic agents are *B. henselae*, *B. Quintana*
- Typically occurs in HIV (with CD4 counts < 200/ μ L) or in other immunocompromised patients
- Adheres to and invades red blood cells (RBCs)
- Makes an endothelial cell-stimulating factor: proliferation of both endothelial cells and blood vessels
- Clinical
 - Four cutaneous patterns
 - Erythematous papules and nodules that are non-blanching
 - Violaceous nodule (similar to Kaposi's sarcoma)
 - Violaceous lichenoid plaque
 - Subcutaneous nodule that may ulcerate

- Other areas of the body affected by BA: brain, bone, bone marrow, lymph nodes, gastrointestinal tract, respiratory tract, spleen and liver
- Peliosis hepatitis
 - Blood-filled cysts in liver of AIDS patients (occasionally are found in spleen)
 - Nausea, vomiting, diarrhea, and fever with hepatosplenomegaly
- Diagnosis:
 - Histology
 - Bacilli stain with modified Warthin-Starry stain (silver-based)
 - Vascular proliferation with small vessels arranged in clusters; epithelial collar-like may be observed
 - Chest x-ray and CT: pulmonary nodules
- Treatment
 - Erythromycin, doxycycline
 - May get Jarisch-Herxheimer reaction:
 - Self-limited reaction to therapy
 - Seen after treatment of syphilis, borreliosis, brucellosis, typhoid fever, trichinellosis, leptospirosis, leprosy, Lyme disease, relapsing fever (epidemic)
 - Fever, malaise, nausea/vomiting
 - Exacerbation of secondary rash
 - Occurs 8 hours after the first injection
 - Resolves within 24 hours

TRENCH FEVER

- Caused by *B. quintana* (aerobic, gram-negative bacillus)
- Incubation period of a few days to a month
- Clinical
 - Symptoms begin with chills and fever: relapsing fever every 5 days (also can have single febrile episode occurring for 3 to 5 days or persistent fever lasting 2 to 6 weeks)
 - Headaches, neck and back pain
 - Groups of erythematous macules or papules measuring 1 cm or less
 - Spread by human body louse (*Pediculus humanus corporis*)
- Diagnosis
 - Polymerase chain reaction (PCR)
- Histology: perivascular infiltrate, organisms are not visible
- Treatment: doxycycline, erythromycin

OROYA FEVER (CARRION'S DISEASE) AND VERRUGA PERUANA

- Caused by *B. bacilliformis*
- Vector: sand fly (*Lutzomyia verrucarum*)
- Clinical

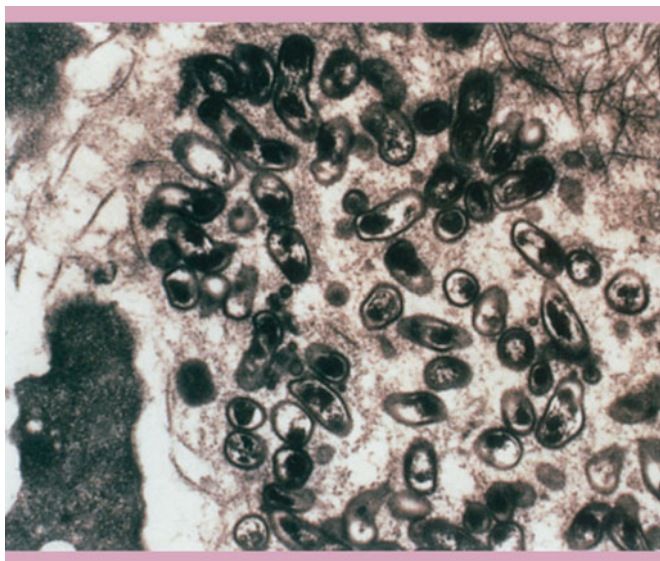


FIGURE 18-10 Bacillary angiomatosis. (Reprinted with permission from Connor DH et al. *Pathology of Infectious Diseases*. Stanford, CT: Appleton & Lange; 1997, p. 408.)

- Fever begins 3 to 12 weeks after bite
- Acute form: fevers, headache, hepatosplenomegaly, hemolytic anemia (80% of RBCs infected), depressed CD4 counts
- Chronic form: verruga peruana (Fig. 18-11)
 - Small nodules form and subsequently become larger
 - Vascular miliary, nodular and mular lesions form (resemble pyogenic granuloma)
 - Can ulcerate, bleed, and heal by fibrosis over several months
 - Various stages may occur together
- Diagnosis:
 - Histology: Rocha-Lima bodies: purple cytoplasmic inclusion bodies in endothelial cells
 - Hemolytic anemia, thrombocytopenia, and elevated liver function studies
- Treatment: chloramphenicol or doxycycline

BRUCELLOSIS (MEDITERRANEAN FEVER, MALTA FEVER, GASTRIC REMITTENT FEVER, AND UNDULANT FEVER)

- *Brucella abortus*, *B. melitensis*, *B. suis*, and *B. canis* (aerobic gram-negative coccobacilli)
- Aerosol transmission as well as through breaks in the skin, mucous membranes, conjunctiva, and respiratory and GI tracts
- Infections are seen in occupations with direct or indirect exposures to animals, such as the meat-packing industry, or from unpasteurized dairy products (goat cheese)
- Incubation is between 1–8 weeks
- Cell wall lipopolysaccharide (LPS): principal virulence factor that enters macrophages
- Infects organs of the reticuloendothelial system (i.e., liver, spleen, bone marrow)



FIGURE 18-11 Verruga peruana. (Reprinted with permission from Connor DH et al. *Pathology of Infectious Diseases*. Stanford, CT: Appleton & Lange; 1997, p. 434.)

- Host response results in tissue granulomas and visceral microabscesses
- Clinical
 - Acute fever, malaise, arthralgias
 - Cutaneous signs: rare granulomas, ulcerations, petechiae, purpura, and erythema nodosum
 - Endocarditis
 - Sacroiliitis, epididymo-orchitis in males
 - Meningitis
- Diagnosis:
 - Agglutination titers for anti-O-polysaccharide antibody
 - Culture (bone marrow culture much more sensitive than blood culture)
 - Immunoglobulin G (IgG) by ELISA
 - Anemia, thrombocytopenia, pancytopenia in 6% of patients
 - Elevated liver enzymes
 - Bone marrow: erythrophagocytosis
 - CSF reveals pleocytosis, elevated protein levels
 - Echocardiogram to evaluate for endocarditis
- Treatment
 - Doxycycline and rifampin or trimethoprim-sulfamethoxazole (TMP-SMZ) plus rifampin
 - Drain pyogenic joint effusions or rare paraspinal abscesses

Leptospirosis (Weil Disease or Icteric Leptospirosis)

- *Leptospira interrogans* (spirochete)
- Incubation period is usually 7–12 days
- Infects many types of mammals: cats, dogs, cattle, pigs, squirrels
- Transmitted via infected urine and then through contact with contaminated water and soil
- Over half of cases in the United States occur in Hawaii
- Clinical
 - Two distinct presentations
 - Septicemic: organism may be isolated from blood cultures, CSF, and most tissues; patients may have myalgias, weakness as well as meningitis like symptoms (headache, photophobia)
 - Immune: occurs after a few days of improvement following the septicemic stage.
 - Occurs as a result of an immune reaction to the infection
 - Circulating antibodies may be detected or the organism may be isolated from urine; it may not be recoverable from blood or CSF
- Subclinical meningitis with headaches, fever, petechiae
- Cutaneous lesions: macular or maculopapular eruption with erythematous, urticarial, petechial, or desquamative lesions, jaundice (90% of

- patients manifest a mild anicteric form of the disease)
- Vasculitis of capillaries: petechiae, intraparenchymal bleeding, and bleeding along serosa and mucosa
- Organ involvement: direct hepatic injury (jaundice, hepatosplenomegaly, nausea and vomiting), alveolar capillary injury, renal tubular necrosis, myocarditis and coronary arteritis
- CSF: \pm encephalitis
- Syndromes occasionally based on species type
 - *L. autumnali*: Pretibial fever (Fort Bragg fever): fevers, pretibial erythema, and ocular symptoms
 - *L. grippotyphosa*: Gastrointestinal symptoms
 - *L. pomona* or *L. canicola*: aseptic meningitis;
 - *L. icterohaemorrhagiae*: jaundice (83% of patients)
- Weil syndrome: profound jaundice, renal dysfunction, hepatic necrosis, pulmonary dysfunction, and hemorrhagic diathesis
- Diagnosis
- Serologies: microscopic agglutination test (MAT): four-fold increase
- Indirect hemagglutination assay (IHA):
 - Dark-field microscopy of blood or rising antibodies
 - Culture: blood, CSF, urine
- Treatment: tetracyclines or penicillin (possible Jarisch-Herxheimer reaction)

TICK-BORNE BACTERIAL INFECTIONS

Tularemia (Ohara's Disease, Deer Fly Fever)

- *Francisella tularensis* (gram-negative coccobacillus)
- Vectors: hard tick (*Dermacentor andersoni*) or deer fly (*Chrysops discalis*)
- Reservoir: rabbits ("rabbit fever" common in hunters)
- Incubation period of 3–4 days
- Clinical
 - Eight forms: depend on mode of transmission: ulceroglandular (most common), glandular, oculoglandular, oropharyngeal, pulmonary, typhoidal, meningeal, chancriform
 - Intracellular parasitism of reticuloendothelial system of humans
 - Infection common in hunters after infected animal exposure via vectors
 - Ulceroglandular (70–80% of cases)
 - Organism enters through a scratch or abrasion.
 - Tender papule that ulcerates with sporotrichoid spread
 - Regional lymphadenopathy

- Typhoidal (10–15% of cases) severe form with pneumonia, fever, myalgias
- Diagnosis:
 - Blood cultures: usually normal
 - Serologic testing: enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR)
- Treatment: aminoglycosides (streptomycin)
 - Considered by the CDC to be a viable weapon of bioterrorism (Category A)

Lyme Disease (Fig. 18-12)

- Caused by the spirochete *Borrelia burgdorferi*
- Vector: *Ixodes* ticks (hard ticks)
- Eastern/midwestern United States: *I. scapularis*, *I. dammini*
- Northwestern United States: *I. pacificus*
- Europe: *I. ricinus* and *I. persulcatus*
- Clinical
 - Stage 1: early localized
 - Erythema migrans (EM) occurs in up to 80% of cases
 - Erythematous macule or papule at site of the tick bite, can have central clearing
 - Expanding figurate erythema occurs over days to weeks
 - Typically resolves in about one month



FIGURE 18-12 Lyme disease. (Reprinted with permission from Connor DH et al. *Pathology of Infectious Diseases*. Stanford, CT: Appleton & Lange; 1997, p. 637.)

- Stage 2: early disseminated disease
 - Hematogenous spread
 - Lymphocytic meningitis, cranial neuropathy, carditis (heart block, arrhythmias), and rheumatologic changes (arthralgias, oligoarthritis)
 - Borrelial lymphocytoma: bluish red nodular swelling that is almost always on the lobe of the ear or the areola of the nipple
- Stage 3: late Lyme disease
 - Acrodermatitis chronica atrophicans (ACA)
 - 20% of patients have history of untreated erythema migrans
 - Develops 6 months to 10 years later
 - Inflammatory phase (early)
 - Edema and erythema, usually on the distal extremities
- Atrophic phase (late)
- 5–10% of patients develop scleroderma-like plaques
 - Loss of subcutaneous fat, with thin, atrophic, and dry skin
 - Neurologic changes (meningitis, encephalitis)
- Diagnosis
 - Antibody titer (antibodies take 4–6 weeks to develop and thus, are not usually present at the time of the rash)
 - Confirm positive ELISA antibody titers with PCR
 - False-positive results of IFA or ELISA can occur because of cross-reactivity with *Treponema pallidum*, and other spirochetal agents
 - Histology: presence of telangiectasias and cellular infiltrates of lymphocytes with admixed plasma cells; ACA demonstrates striking epidermal atrophy
- Treatment
 - Doxycycline or amoxicillin
 - Pediatric patients: erythromycin

Rickettsioses

- Obligate intracellular gram-negative coccobacilli
- Transmitted to humans by arthropods
- Spotted fever group
 - Rocky Mountain spotted fever
 - Rickettsial pox
 - Boutonneuse fever
- Typhus group
 - Louse-borne (epidemic) typhus
 - Brill-Zinsser disease (i.e., relapsing louse-borne typhus)
 - Murine (endemic or flea-borne) typhus
- Other rickettsial diseases
 - Tsutsugamushi disease (i.e., “scrub typhus”)
 - Q fever: *Coxiella burnetii*
 - Ehrlichia

ROCKY MOUNTAIN SPOTTED FEVER

- *Rickettsia rickettsii* (obligate intracellular gram -coccobacilli)
- Disease commonly found in North Carolina and Oklahoma which account for one third of total cases reported; other areas outside of the United States include Canada, Mexico, Central America, Colombia, and Brazil
- Vectors
 - Eastern United States: wood tick (*Dermacentor andersoni*)
 - Western United States: dog tick (*Dermacentor variabilis*)
- Clinical
 - Triad: fever, headache, and rash (1 to 2 weeks after tick bite)
 - Multisystem involvement is common
 - Skin lesions
 - Appear two to four days following fever
 - Blanchable macular rash that starts on extremities and spreads to trunk (centripetal)
 - Face usually spared; involvement of the scrotum or the vulva and palms/soles
 - Erythematous macules that become petechial over a few days.
 - “Spotless” fever in 10% of cases
 - Desquamation occurs as the rash fades
 - Systemic findings: hepatosplenomegaly, myocarditis, thrombocytopenia, CNS involvement (confusion, lethargy, ataxia, and seizures)
 - Rumble-Leede test
 - Multiple petechiae appear where sphygmomanometer or tourniquet is placed
- Diagnosis
 - Elevated liver function tests
 - Blood cultures
 - Indirect fluorescent antibody
 - Direct immunofluorescence
 - Immunoperoxidase staining
 - Latex agglutination
 - Complement fixation
 - Giemsa stain
 - Lumbar puncture
 - Weil-Felix assay: agglutination of OX-strains of *Proteus vulgaris* with suspected rickettsia
- Treatment
 - Tetracycline or chloramphenicol (in pediatric patients)
 - Avoid sulfa treatments; symptoms may worsen

RICKETTSIALPOX

- Caused by *R. akari*
- Vector: rodent (house mouse) mite, *Liponyssoides sanguineus* (formerly *Allodermanyssus sanguineus*)

- Most common in boroughs of New York City (Brooklyn, Queens), found commonly in urban areas
- Incubation period is 10–21 days
- Clinical
 - Papular skin lesions appear at the bite site and then become vesicular with surrounding erythema
 - Dries and forms a black eschar; no scarring
 - Sudden onset of high-grade fever and chills (3 days after skin lesions), headaches, and myalgias
 - Mild and self-limited disease which persists for about a week
- Diagnosis:
 - Cultures from blood
 - Direct fluorescent antibody test of biopsies from skin lesions
 - Immunofluorescence antibody (IFA) testing
 - Complement fixation
 - Histology: mononuclear cell infiltration and necrosis of the dermis and epidermis. Perivascular inflammation with thrombi and extravasation of red blood cells.
 - Giemsa stain of tissue: small coccobacillary intracellular bacteria
- Treatment
 - Self-limited disease
 - Doxycycline or chloramphenicol, quinolones

BOUTONNEUSE FEVER (MEDITERRANEAN FEVER)

- Causative agent is *R. conorii*
- Vector: *Rhipicephalus sanguineus* (brown dog tick)
- Incubation time of BF is usually 4–15 days
- Clinical
 - Fever
 - Exanthem: erythematous papules, mainly on the lower limbs
 - Tache noire (eschar, necrotic plaque) at the site of the tick bite
 - Malignant form
 - Criteria: requires two laboratory abnormalities (thrombocytopenia, increased creatinine level, hyponatremia, hypocalcemia, hypoxemia) and two clinical criteria (purpuric rash, stupor, pneumonia, bradycardia, coma, jaundice, gastrointestinal bleeding)
 - More common in patients with underlying disease or in elderly persons
 - Disease progression: acute stage is from the second to 14th day of the illness; convalescent stage starts from the 21st day
- Diagnosis:
 - Immunofluorescent antibody: direct immunofluorescence of cutaneous biopsy specimens (during active disease)
 - Culture

- Enzyme-linked immunosorbent assay (ELISA): detects antibodies to lipopolysaccharides (LPS) of *R. conorii*
- Treatment: tetracyclines together with chloramphenicol and quinolones

Typhus Group

- Three main forms of typhus: epidemic typhus; rat-flea or endemic typhus, and scrub typhus.
- Diagnosis
 - Actual isolation and culture of *rickettsiae* are difficult
 - Serologic tests for antibodies
 - Indirect immunofluorescence assay (IFA)
 - Enzyme-linked immunosorbent assay (ELISA)
 - Indirect immunoperoxidase
 - Weil-Felix test
 - Polymerase chain reaction (PCR): serum or skin biopsy
 - Complement fixation (CF)
- Treatment: doxycycline, chloramphenicol

EPIDEMIC TYPHUS

- Caused by *R. prowazekii*
- Vector: human body louse (*Pediculus humanus corporis*)
- Humans are the natural reservoir
- Incubation period of 7 to 14 days
- Clinical
 - Fever, headache
 - Maculopapular rash occurs on days 4 to 7
 - Begins on the axilla and trunk and spreads peripherally
 - Can become hemorrhagic with necrosis
 - Mortality is high in untreated elderly patients
 - Brill-Zinsser disease: mild recurrence of disease: can occur months, years, or even decades after treatment

MURINE TYPHUS (ENDEMIC TYPHUS)

- Caused by *R. typhi*
- Vectors: rat or cat flea (*Xenopsylla cheopis*, *Ctenocephalides felis*)
- Incubation of 6 to 18 days
- Clinical
 - Erythematous macular eruption without becoming hemorrhagic or necrotic following fever

Scrub Typhus (Tsutsugamushi Fever)

- *Orientia tsutsugamushi* (formerly *Rickettsia tsutsugamushi*); it has a different cell wall structure and genetic composition than that of the rickettsiae
- Vector: trombiculid mite (larval stage of a chigger): *Leptotrombidium akamushi* and possibly *L. deliense*
- Incubation period is 5–20 days
- Clinical

- Headaches, shaking chills, lymphadenopathy, conjunctival injection, fever
- Painless papule develops at site of bite, and then a central necrosis results with formation of an eschar
- Five to eight days after infection, dull red rash on trunk and extending to the extremities
- Pneumonitis or encephalitis can occur
- Hepatosplenomegaly
- Regional lymphadenopathy

Ehrlichiosis

- Due to gram-negative organisms that resemble *Rickettsia*
- Human monocytic ehrlichiosis (HME): *Ehrlichia chaffeensis*
- Human granulocytic ehrlichiosis (HGE): *E. phagocytophilia*
- Vector: Lone Star tick (*Amblyoma americanum*) or deer tick (*Ixodes persulcatus*)
- Infects mononuclear cells and granulocytes
- Clinical
 - Rash is rare in ehrlichiosis; however, can develop maculopapular lesions following fever
 - Rare renal failure and encephalopathy
 - Lymphadenopathy may be present
- Diagnosis:
 - Histology: characteristic morulae in the cytoplasm of leukocytes
 - Neutropenia, lymphocytopenia, or thrombocytopenia
 - Elevated immunoglobulin G (IgG) immunofluorescent antibody (IFA) *Ehrlichia* titer
- Treatment: tetracyclines; chloramphenicol is not effective in ehrlichiosis

SEXUALLY TRANSMITTED BACTERIAL INFECTIONS

Gonorrhea (Fig. 18-13)

- *Neisseria gonorrhoeae* (gram-negative intracellular aerobic diplococcus)
- Clinical
 - Men: urethritis; women: dyspareunia, bleeding or discharge
 - Neonates: bilateral conjunctivitis (ophthalmia neonatorum) after vaginal delivery from an infected mother
 - Acute perihepatitis with hepatic capsular adhesions (Fitz-Hugh-Curtis syndrome)
 - Dissemination: arthritis dermatitis syndrome (1–3% of cases)
 - Septic arthritis: knee is most common site; polyarthralgia with pain, tenderness

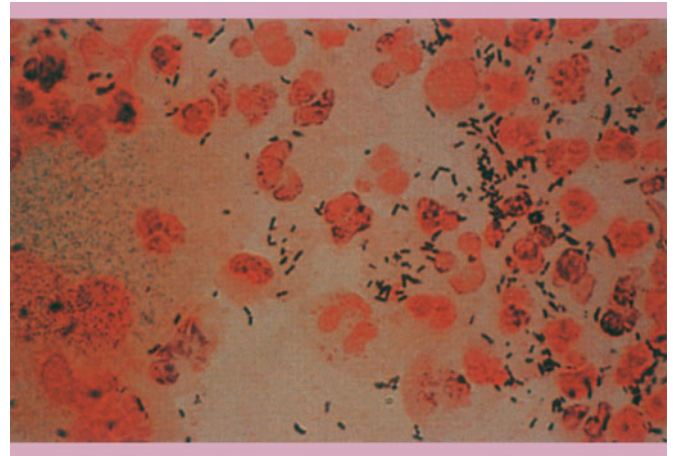


FIGURE 18-13 Gonorrhea. (Reprinted with permission from Connor DH et al. *Pathology of Infectious Diseases*. Stanford, CT: Appleton & Lange; 1997, p. 686.)

- Rare gonococcal meningitis and endocarditis
- Skin findings: maculopapular, pustular, necrotic, or vesicular lesions; face, scalp, and mouth are usually spared.
- Diagnosis:
 - Culture on chocolate agar
 - Gram stain
 - Fluorescein-conjugated monoclonal antibodies, enzyme-linked immunoassays
- Treatment: ceftriaxone intramuscular, cefixime, ciprofloxacin

Granuloma Inguinale (Fig. 18-14)

- *Klebsiella granulomatis* (gram-negative rod), formerly *Calymmatobacterium granulomatis*
- Clinical
 - Four types of skin lesions:
 - *Ulcerovegetative* (most commonly seen)
 - ▲ Painless, beefy red ulcers with clean, friable bases and distinct, raised/rolled margins
 - ▲ Autoinoculation is common
 - *Nodular*
 - ▲ Pruritic, soft, red nodules that ulcerate at the site of inoculation
 - ▲ Pseudobubo: nodule appears clinically as a lymph node
 - *Cicatricial*
 - ▲ Dry ulcers that progress into scarring plaques
 - ▲ Lymphedema may be present
 - *Hypertrophic or verrucous* (relatively rare)
 - Vegetating soft masses



FIGURE 18-14 Granuloma inguinale. (Reprinted with permission from Connor DH et al. *Pathology of Infectious Diseases*. Stanford, CT: Appleton & Lange; 1997, p. 567.)

- Diagnosis:
 - Culture not possible
 - Smear or biopsy with Wright, Giemsa or Warthin-Starry (silver) stain: Donovan bodies: intracytoplasmic bipolar staining, safety pin-shaped, inclusion bodies seen in histiocytes
 - Histology: acanthosis, dermis with histiocytes and plasma cells, large and vacuolated macrophages with intracellular bacilli (i.e., Donovan bodies)
- Treatment: doxycycline or trimethoprim/sulfamethoxazole

Lymphogranuloma Venereum (Fig. 18-15)

- Caused by *Chlamydia trachomatis* L1, L2 (most common), L3 serotypes
- Incubation period of 3–21 days
- Clinical
 - 3 stages:
 - *First stage*: small papule usually not seen, lasts 1 week, painless
 - *Second stage*: buboes (painful lymph nodes) after 2 to 6 weeks; groove sign: enlargement of the nodes above (inguinal) and below (femoral) the inguinal ligament (poupart's)
 - *Third stage*: fistulas seen more often in women, proctocolitis, results in scarring/chronic lymphatic obstruction (acute rectal syndrome)
- Diagnosis:
 - Complement fixation test with titer of 1:64
 - Culture



FIGURE 18-15 Lymphogranuloma venereum. (Reprinted with permission from Freedberg IM et al. *Fitzpatrick's Dermatology in General Medicine*, 6th ed. New York: McGraw-Hill; 2003, p. 2199.)

- Immunofluorescent testing with monoclonal antibodies
- Treatment: doxycycline; alternative is erythromycin

Chancroid (Fig. 18-16)

- Caused by *Haemophilus ducreyi* (gram-negative bacillus)
- The bacteria secretes a cyto-lethal distending toxin (HdCDT): inhibits cell proliferation and induces cell death
- Clinical
 - Soft chancre
 - Painful ragged punched-out ulcers, undermined borders, covered by a grayish fibrinous membrane
 - Lymph node involvement mostly unilateral and can rupture
 - Bubo: tender, fixed, inguinal lymphadenopathy
- Diagnosis
 - Gram staining: organisms in a “school-of-fish” pattern
 - Culture
 - Immunochromatography: monoclonal antibodies to the hemoglobin receptor of *H. ducreyi*, hgbA
- Treatment
 - Azithromycin 1 g PO single dose, ceftriaxone 250 mg IM single dose, erythromycin 500 mg PO qid for 7 days, or ciprofloxacin 500 mg PO bid for 3 days.
 - Buboes should be drained

Syphilis

- Caused by *Treponema pallidum* (microaerophilic spirochete)



FIGURE 18-16 Chancroid. (Reprinted with permission from Freedberg IM et al. *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003; p. 2195.)

- Clinical
 - Primary
 - Occurs after incubation of approximately 3 weeks
 - Highly infectious painless chancre (ulcerated lesion with a surrounding red areola)
 - Lasts 10 to 14 days
 - Bubo
 - ▲ Enlarged, nontender lymph nodes
 - Secondary
 - Occurs usually one month after chancre presents
 - Hair: alopecia (“moth eaten”), caused by papular follicular syphilids, localized patches to total alopecia
 - Mucous membrane:
 - ▲ Condyloma lata: infectious papules and small plaques develop at the mucocutaneous junctions and intertriginous areas
 - ▲ Pharyngitis
 - ▲ Mucous patches: silver-gray erosions with a red areola
 - Skin: bilaterally symmetric discrete round macules on the trunk and proximal extremities (often affecting palms and soles); can become necrotic
 - Ocular: anterior uveitis
 - Latent syphilis
 - Follows resolution of the secondary stage
 - Only evidence is positive serologic test for syphilis
 - Categories
 - ▲ Early latent: < 1 year’s duration
 - ▲ Late latent: ≥ 1 year’s duration or of unknown duration (seroreactivity, in the absence of symptoms, greater than 2 years after inoculation)
- Tertiary
 - Seroreactivity greater than 2 years with symptoms
 - Gummas: granulomas of skin and bone
 - Neurologic (neurosyphilis): may be asymptomatic or present as a subacute meningitis
 - ▲ Tabes dorsalis: demyelination of the posterior columns, dorsal roots, and dorsal root ganglia (e.g., ataxic wide-based gait and foot slap)
 - ▲ Argyll-Robertson pupil: small, irregular pupil, normal accommodation but abnormal light response (Romberg sign)
 - Cardiovascular: aortic aneurysm, aortitis
- Congenital syphilis caused by transplacental transmission of spirochetes
 - Early (< 2 years of age)
 - ▲ Mucocutaneous changes:
 - △ Snuffles: rhinitis (nasal fluid is highly infectious)
 - △ Rhagades (Parrot lines): depressed linear scars radiating from the orifice of the mouth
 - △ Condyloma lata and mucous patches
 - △ Hepatomegaly
 - ▲ Bone changes:
 - △ Cranio tabes: reduction in mineralization of the skull, with abnormal softness of the bone
 - △ Pseudoparalysis of Parrot: child keeps limb still secondary to pain from osteochondritis
 - △ Osteochondritis: sawtooth x-ray lesion
 - ▲ Skin:
 - △ Copper-colored papulosquamous eruption, desquamative rash
 - △ Hematologic: jaundice, thrombocytopenia
 - Late (> 2 years of age)
 - ▲ Interstitial keratitis: inflammation of the corneal stroma
 - ▲ Corneal opacities
 - ▲ Hutchinson teeth: peg-shaped incisors
 - ▲ Mulberry molars: poorly developed cusps
 - ▲ Saddle nose: secondary to gummatous periostitis
 - ▲ Syphilitic pemphigus: congenital bullae with purulent fluid on palm
 - ▲ Bone changes:
 - △ Saber shin: anterior bowing of tibia

- △ Frontal bossing
 - △ Higomenaki's sign: unilateral sterno-clavicular enlargement
 - △ Bulldog jaw
 - △ Clutton joints (arthritis of both knees)
 - ▲ Recurrent arthropathy
 - ▲ Cranial nerve VIII deafness
- Diagnosis
 - Histology: often with psoriasiform and lichenoid changes and perivascular infiltration, chiefly by lymphocytes, plasma cells, and macrophages; may see spirochetes with modified Steiner or Warthin-Starry stains (silver based)
 - Identification of *T. pallidum* in lesions on tissue:
 - Dark-field microscopy: immediate result
 - DFA-TP (direct fluorescence antibody test): direct fluorescent antibody *T. pallidum*, 1 to 2 days
 - immunohistochemical stains for *T. pallidum*
 - *Nontreponemal serology screening*
 - Venereal Disease Research Laboratory (VDRL) test: measures IgM and IgG antibody directed against a cardiolipin lecithin-cholesterol antigen; not specific for *T. pallidum*; used to follow response to therapy (lower titers with successful treatment)
 - Prozone effect:
 - May cause a false-negative reaction
 - Occurs when the reaction is overwhelmed by antibody excess and may happen in late primary or secondary syphilis
 - Should dilute the serum to at least a 1/16 dilution
 - Rapid plasma reagin (RPR)
 - Develops 1 to 4 weeks after chancre
 - Fourfold decline in titer by 3 months following treatment
 - False-positive RPR results occur in 1% to 2% of the normal population.
 - *Treponemal tests*
 - FTA-ABS: fluorescent treponemal antibody absorption
 - ▲ Reactive 4 to 6 weeks after infection
 - ▲ Remains reactive for many years
 - ▲ Does not indicate response to therapy
 - ▲ Does not distinguish between syphilis and other treponematoses
 - ▲ Antibody (IgM and IgG) directed against *T. pallidum*
 - MHA-TP: microhemagglutination assay *T. pallidum* test
 - ▲ Remains reactive for life
 - ▲ Not recommended for monitoring reinfection or the efficacy of treatment

- ▲ Chest x-ray for patients with tertiary syphilis to screen for aortic dilation
- ▲ Lumbar puncture: in patients with latent syphilis, if treatment has failed or the time course of disease is unknown and if the patient is known to also have HIV.

- Treatment
 - Penicillin 2.4 million units IM
 - Jarisch-Herxheimer reaction (see above)

MYCOBACTERIA

Leprosy (Hansen's Disease)

- Chronic granulomatous infection that affects skin and nerves
- Causative organism is *Mycobacterium leprae* (intracellular acid-fast gram-positive bacillus)
- Transmission: respiratory, human to human, armadillos, and sphagnum moss
- Humans are the primary reservoir of *M. leprae*
- Bimodal age distribution, with peaks at ages 10–14 years and 35–44 years
- Incubation: up to 5 years and may be 20 years or longer
- Clinical
 - *Neurological*
 - Acral distal symmetric anesthesia
 - Palsies of cranial nerves V and VII
 - Nerve enlargement
 - Predilection for superficial nerves (bacteria prefers lower temperatures)
 - Great auricular, ulnar, median, superficial peroneal, sural, and posterior tibial nerves (most commonly affected)
 - Anesthetic skin lesions (sensation to temperature is lost first)
 - *Cutaneous*: varies based on type of infection
 - *Ocular*: lagophthalmos (inability to close the eye/involvement of cranial nerve [CN] VII branches), reduced corneal reflex and reduced blinking [ophthalmic branch of the trigeminal nerve (CN V2)]
 - *Classification of leprosy types*
 - Depends on the level of host cell-mediated immunity
 - TT (polar tuberculoid) ↔ BT (borderline tuberculoid) ↔ BB (borderline) ↔ BL (borderline lepromatous) ↔ LLs (subpolar lepromatous), LLp (polar lepromatous)
 - Levels are not static: patients can move through spectrum of disease through upgrading or downgrading reactions
- *Indeterminate leprosy (IL)*
 - Early form, usually no sensory loss

- One to a few hypopigmented, macules that typically heal spontaneously
- *Tuberculoid leprosy (TT)*
 - Paucibacillary
 - Predominance of CD4⁺ cells: cell-mediated immunity can localize infection
 - T_H1 (proinflammatory) profile: interleukin 2 (IL-2), interferon- δ (IFN- δ), and IL-12
 - Clinical
 - Erythematous large plaque with well-defined borders and atrophic center, anesthetic and anhidrotic, scalp and intertriginous areas are usually spared
 - Tender, thickened nerves
 - Histology
 - Resembles tuberculosis
 - Two histologic patterns
 - Mature epithelioid tubercles surrounded by lymphoid mantles
 - Many large Langhans' giant cells, fibrinoid necrosis, occasional areas of caseation necrosis, and exocytosis (associated with TT upgraded from BT)
 - Tissue may be negative for AFB owing to paucibacillary nature
 - Prognosis: spontaneous resolution or progression to borderline leprosy
- *Borderline tuberculoid leprosy (BT)*
 - Host response is insufficient for self-cure
 - Multiple (occasionally solitary) anesthetic asymmetric annular plaques with satellite papules
 - Symmetric nerve enlargement or palsy
 - Histology: epithelioid tubercles, fewer lymphocytes than in TT; usually negative for AFB
- *Borderline leprosy (BB)*
 - Most unstable type: patients quickly up- or downgrade
 - Multiple annular plaques with indistinct borders compared with TT lesions; can have classic dimorphic lesions
 - Mild anesthesia
 - Histology
 - Granulomas have epithelioid differentiation; no giant cells or lymphoid mantle
 - AFB are found easily
- *Borderline lepromatous leprosy (BL)*
 - Host resistance too low to restrain bacillary proliferation
 - Destructive inflammation in nerves still occurs
 - Dimorphic lesions: annular patches with poorly margined borders (lepromatous-like) and sharply margined inner ones (tuberculoid-like)
 - Annular punched-out-appearing lesions also occur
 - Histology
 - Granulomas with lymphocytes and foamy macrophages
 - Nerves with inflammatory cell infiltration; bacilli and globi (*M. leprae* within multinucleate Virchow giant cells from histiocytes)
- Patients remain in this stage, improve, or regress
- *Lepromatous leprosy (LL)*
 - Multibacillary
 - Predominance of CD8⁺ cells
 - T_H2 (anti-inflammatory) profile: IL-4 and IL-10
 - Lack of cell-mediated immunity permits progression of the infection
 - HLA-DQ1 and TLR2 gene mutations have been associated with LL
 - Clinical (Fig. 18-17)
 - Poorly defined symmetric skin-colored plaques and nodules, begin as pale macules
 - Anhidrosis
 - Diffuse dermal infiltration
 - Leonine facies: widening of the nasal root
 - Madarosis: lateral alopecia of the eyebrows and lashes
 - Slow and progressive nerve involvement, acral distal symmetric anesthesia
 - Testicular infection: invasion of the seminiferous tubules causing sterility
 - Ocular involvement: photophobia, glaucoma, blindness
 - Oral involvement: lepromas of the hard and soft palates
 - Aseptic necrosis and osteomyelitis



FIGURE 18-17 Lepromatous leprosy. (Courtesy of Dr. Steven Mays.)

- Subpolar lepromatous (LLs): can develop reversal reactions and erythema nodosum leprosum
- Polar lepromatous (LLp): develops erythema nodosum leprosum
- Histoid leprosy (HL): clinical variant of LL, occurs as a result of resistance to monotherapy; multi-bacillary lesion with spindle-shaped cells resembling fibrocytes without globi
- Histology: Grenz zone (upper area of dermis is spared), foamy macrophages with globi (Virchow cells)
- Untreated LL is progressive, it does not revert to the less severe borderline or tuberculoid types
- *Relapsing leprosy*
 - Multibacillary patients who are noncompliant or develop drug resistance
 - Early relapses (occurring within 3.5 years after stopping treatment) are probably due to insufficient treatment, and late relapses (occurring more than 3.5 years after stopping treatment) to persisting bacilli or to reinfection
 - Clinical
 - Recurrence of initial presentation
 - Florid dermatofibroma-like lesions (histioid leprosy)
 - Develop a reactionary state: destructive inflammatory processes
- *Jopling's type 1 reversal reaction* (lepra reaction)
 - Delayed-type hypersensitivity reaction, leading cause of neurological impairment in patients with leprosy
 - Affects 30% of patients with borderline leprosy
 - Patients either upgrade to a more resistant state, remain unchanged, or downgrade to a less resistant state
 - Clinical
 - Abrupt conversion of previously quiescent plaques to tumid lesions and/or development of new tumid lesions in clinically normal skin
 - Dusky purple erythematous plaques
 - Iritis and lymphedema (elephantiasis graecorum)
 - Neuritis
- *Jopling's type 2 reaction* (erythema nodosum leprosum)
 - Often in LL but also in BL before, during, or after therapy
 - Clinical
 - Crops of tender bright pink nodules in clinically normal skin
 - Fever, anorexia, and malaise
 - Upper and lower extremities, facial lesions in 50%
 - Arthralgias
 - Neutrophilic leukocytosis
 - Abrupt fall in hematocrit
- *Lucio reaction*
 - Occurs in untreated diffuse lepromatous leprosy and/or relapsing leprosy
 - Seen in Mexico and the Caribbean
 - Latapi's lepromatosis: diffuse nonnodular lepromatous leprosy with hemorrhagic infarcts
 - Telangiectases
 - Nasal septum perforation
 - Total alopecia of the eyebrows and lashes
 - Acral distal symmetric anesthesia
 - Crops of necrotic lesions
 - Painful ulcerations of the skin
 - Histology: ischemic necrosis secondary to endothelial parasitization by AFB; thrombosis in deep vessels
 - Treatment for Lucio reaction: rifampin
- Laboratory changes
 - Hyperglobulinemia
 - False-positive serologic test for syphilis
 - Anemia of chronic disease
 - Mild lymphopenia
 - Elevated serum lysozyme and angiotensin-converting enzyme
 - Proteinuria due to focal glomerulonephritis in ENL
 - Testicular involvement in LL males manifests as high serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) but low testosterone
 - Lepromin skin testing (Mitsuda test): intradermal injection of *M. leprae*, positive reaction occurs if a 5 mm or greater nodule appears 2–3 weeks following injection (usually positive in TT and BT leprosy while BB through LLp are negative)
 - Not useful in diagnosis, indicates host resistance
 - Helps in classification
- Treatment
 - Treatment may last from 6 months to 2 years. After 1–2 weeks of treatment, patients are considered noninfectious
 - *Paucibacillary (tuberculoid) disease*
 - Dapsone (bacteriostatic) 100 mg daily
 - Supervised rifampin (bactericidal) 600 mg monthly for 6 months
 - *Multibacillary (lepromatous) disease*
 - Dapsone 100 mg daily + supervised rifampin 600 mg monthly + clofazimine (bacteriostatic) 50 mg daily (unsupervised) and 300 mg monthly (supervised) for 2 years
 - Alternative combination of minocycline (bactericidal) 100 mg daily + rifampin 600 mg daily for 2 to 3 years, followed by monotherapy
 - *Reversal reactions*
 - Prednisone (0.5 to 1.0 mg/kg per day)

- Prevents permanent nerve damage
- Minimum of 6 months
- *Erythema nodosum leprosum*
 - Thalidomide is the treatment of choice
 - Prednisone + clofazimine 200 mg daily

TUBERCULOSIS

- Caused by *Mycobacterium tuberculosis*
 - Aerobic, intracellular, curved bacilli, acid fast
 - Transmitted by airborne droplets
 - Causes epithelioid granulomas with central caseation necrosis
 - Clinical
 - *Multiorgan infection*:
 - Pulmonary: productive cough, fever, and weight loss, hemoptysis or chest pain
 - Meningitis: headache that is either intermittent or persistent, mental status changes
 - Skeletal: spine (Pott disease), arthritis: hip or knee
 - Genitourinary: flank pain, dysuria, or frequency
 - Gastrointestinal TB: nonhealing ulcers
 - *Cutaneous TB*
 - Verrucosa cutis
 - ▲ Direct inoculation
 - ▲ Prior infection
 - ▲ Purplish or brownish-red warty growth
 - Lupus vulgaris
 - ▲ Hematogenous spread
 - ▲ Persistent and progressive
 - ▲ Sharply defined reddish brown papule, plaques with a gelatinous consistency (apple-jelly color)
 - Cutis orificialis
 - ▲ Autoinoculation into the periorificial skin and mucous membranes
 - ▲ Yellow/red nodule on mucosa that results in ulceration
 - ▲ Patients with advanced TB
 - ▲ Tuberculin sensitivity is strong
 - Scrofuloderma
 - ▲ Direct extension of underlying TB infection of lymph nodes, bone, or joints
 - ▲ Associated with TB of the lungs
 - ▲ Firm, painless lesions that eventually ulcerate with a granular base
 - ▲ Tuberculin sensitivity is strong
 - Metastatic tuberculous abscess (tuberculous gumma)
 - ▲ Occurs following hematogenous spread of mycobacteria to skin in tuberculin-sensitive individuals
 - Laboratory studies
 - Tuberculin skin test: good test for latent infection; intradermal injection of 5 units (0.1 mL) of purified protein derivative (PPD); induration of 5 mm or greater, 48–72 hours following injection; patients with BCG vaccination at birth (10-mm induration or more is a positive result), or if the vaccination was given as an adult (30-mm induration or larger is a positive result)
 - Whole blood assay based on interferon-gamma release (IGRA); tests for latent TB infection
 - Chest radiograph: patchy or nodular upper lobe infiltrates, calcified nodules indicate old infection, small nodular lesions indicate miliary TB
 - Ziehl-Neelsen staining and culture of sputum specimens (3 consecutive days)
 - Skin biopsy: caseating necrosis surrounded by lymphocytes, multi-nucleate giant cells and epithelioid macrophages (organisms may be present within)
 - Treatment
 - Four drug regimen for 2 months
 - Isoniazid
 - Rifampin
 - Pyrazinamide
 - Ethambutol or streptomycin
 - Isoniazid plus rifampin for four more months
- Painless, fluctuant, subcutaneous abscesses form singly or at multiple sites
- Miliary TB
 - ▲ Chronic infection
 - ▲ Hematogenous spread from the primary infection (usually in the lungs) to other tissues
 - ▲ Small red spots that develop into ulcers and abscesses
 - ▲ Immunocompromised patients, e.g., HIV, AIDS, cancer
- Tuberculid: hypersensitivity reactions to tubercle bacillus
 - ▲ Erythema induratum (Bazin disease): recurring subcutaneous nodules that may ulcerate and scar are seen in the posterior calves; tubercle bacilli are not seen; mycobacterial cultures usually are negative; histology shows a lobular panniculitis with vasculitis
 - ▲ Papulonecrotic tuberculid: crops of recurrent necrotic skin papules on knees, elbows, buttocks or lower trunk that heal with scarring after about 6 weeks
 - ▲ Lichen scrofulosorum: lichenoid eruption of small follicular papules in young persons with underlying TB

- Rifampin, pyrazinamide, and ethambutol for the entire 6 months if patient is resistant to isoniazid

Atypical Acid-Fast Mycobacterium (AFB)

- Acid-fast facultative saprophytes and organisms that that do not cause tuberculosis or leprosy
- Usually occur in patients that are immunocompromised
- Categorized according to their production of yellow or orange pigment and their rate of growth
- Group 1
 - Photochromogens (pigmentation on exposure to light)
 - *M. kansasii*, *M. marinum*, *M. simiae*
- Group 2
 - Scotochromogens (pigmentation formed in the dark)
 - *M. scrofulaceum*, *M. szulgai*, *M. gordonae*
- Group 3: nonchromogens (no pigmentation)
 - *M. malmoense*, *M. xenopi*, *M. avium-intracellulare*
- Group 4
 - Fast growers (groups 1, 2, and 3 listed above grow slowly)
 - Grow in three to five days (e.g., *M. fortuitum*, *M. chelonae*, *M. abscessus*)
- Clinical
 - *M. marinum* (Fig. 18-18)
 - Clinical lesion is often called a “fish tank granuloma”
 - Infection occurs when contaminated water is exposed to traumatized skin
 - Usually an isolated nodule on the upper extremity, particularly the hand
 - Lymphangitic spread with several nodules (sporotrichoid spread)
- Treatment: minocycline, clarithromycin, physiotherapy (application of heat)
 - *M. avium-intracellulare* complex (MAC)
 - May cause lung disease in humans
 - Usually infects an immunocompromised host (patients with AIDS)
 - Skin disease rare: plaques, nodules, ulcers
 - *M. ulcerans*
 - An emerging pathogen that causes a Buruli ulcer in humans; the ulcer is deeply undermined, with scarring; lymphedema may result
 - Buruli ulcer is the third most common AFB infection worldwide (second to tuberculosis and leprosy)
 - No satisfactory antimicrobial treatment, often utilize surgery and grafting in treatment
 - Strict growth limited to fatty tissue beneath the dermis
 - *M. kansasii*
 - Pulmonary and extrapulmonary disease in humans similar to tuberculosis; cellulitis, and abscesses; disseminated or pulmonary infection are found in immunocompromised hosts, infection can result in septic arthritis
 - Difficult to treat; does not respond well to drugs
 - Grows well at 37°C
 - *M. scrofulaceum*
 - Causes scrofula (cervical adenitis)
 - Does not respond well to drugs
 - *M. fortuitum* (rapidly growing mycobacteria) (also *M. chelonae* and variety *abscessus*):
 - causes chronic abscesses in humans
 - Primary cutaneous inoculation with possible sporotrichoid spread (linear distribution)
 - Other clinical affects include: keratitis, corneal ulcerations, osteomyelitis, lymphadenitis, and endocarditis
 - May be resistant to treatment
- Diagnosis: stain with carbolfuchsin (basic dye, red in color)
 - Tissue culture
 - Skin biopsy: suppurative granulomas (most characteristic finding) diffuse inflammation with foamy histiocytes, panniculitis, cutaneous abscesses, and necrotizing folliculitis
- Treatment
 - Surgical drainage, debridement, and long term (> 3 mo) treatment with a regimen of several antibiotics used in combination
 - Rifampin
 - Ethambutol
 - Minocycline
 - Trimethoprim and sulfamethoxazole
 - Clarithromycin



FIGURE 18-18 *M. marinum*. (Courtesy of Dr. Asra Ali.)

QUIZ

Questions

- The *chief* difference between impetigo and ecthyma is:
 - Epidermal ulceration
 - Etiological organisms
 - Involvement of resistant organisms
 - Systemic distribution of toxin
 - All of the above
- Bullous impetigo is caused by local production of a toxin produced by _____ that acts to cleave _____.
 - Group A *Streptococcus*, desmocollins
 - Group A *Streptococcus*, desmogleins
 - Staphylococcus aureus*, desmocollins
 - Staphylococcus aureus*, desmogleins
 - Staphylococcus epidermidis*, hemidesmosomes
- Cutaneous infections with Group A *Streptococcus* may lead to _____.
 - Glomerulonephritis
 - Rheumatic fever
 - Scarlet fever
 - A and C only
 - A, B, and C
- When staphylococcal scalded skin syndrome occurs in adults, it is often associated with pre-existing:
 - Complement deficiencies
 - Liver failure
 - Renal insufficiency
 - Tampon use
 - All of the above
- In comparison to ordinary cellulitis, erysipelas is distinguished by _____ erythema and _____ lesions, often occurring on the face or lower extremity.
 - Brighter erythema, well-demarcated lesions
 - Brighter erythema, poorly demarcated lesions
 - Dusky erythema, poorly demarcated lesions
 - Dusky erythema, well-demarcated lesions
 - None of the above
- Wood's lamp examination of erythrasma often demonstrates a "coral-red" fluorescence due to evolution of _____ by the bacteria.
 - Aminolevulinic acid (ALA)
 - Coproporphyrin III
 - Protoporphyrin IX
 - Uroporphyrin I
 - Uroporphyrinogen III
- Cutaneous anthrax is not typically _____.
 - Edematous
 - Fatal
 - Purulent
 - B and C
 - A, B, and C
- Necrotizing fasciitis is characterized by:
 - A need for a deep incisional biopsy for diagnosis
 - Ischemia, thrombosis and tissue necrosis
 - Pain "out of proportion" to physical findings
 - Rapid spread
 - All of the above
- "Hot-tub folliculitis" is caused by:
 - Erysipelothrix rhusiopathiae*
 - Group A *Streptococcus*
 - Pseudomonas aeruginosa*
 - Staphylococcus aureus*
 - Staphylococcus epidermidis*
- Matching exercise:

Part A—Match the following diseases with their corresponding etiological organism:

A. Endemic typhus	1. <i>R. akari</i>
B. Epidemic typhus	2. <i>R. prowasekii</i>
C. Rickettsial pox	3. <i>R. rickettsii</i>
D. Rocky Mountain spotted fever	4. <i>R. tsutsugamushi</i>
E. Scrub typhus	5. <i>R. typhi</i>

Part B—Match the following histopathologic findings with the corresponding disease:

A. Donovan bodies	1. granuloma inguinale
B. Michaelis-Guttman bodies	2. leprosy
C. Mikulicz cells	3. malakoplakia
D. Rocha-Lima bodies	4. rhinoscleroma
E. Virchow cells (globi)	5. verruga peruana

Answers

- A. Of the answer choices, the chief difference between impetigo and ecthyma is the depth of involvement, with ecthyma yielding true epidermal ulceration. Impetigo also tends to involve young children and perioral locations, while ecthyma is more common in teens and adults and is often situated on the lower extremities.
- D. In bullous impetigo, certain forms of *Staphylococcus aureus* (Phage Group 2) may elaborate a toxin which locally cleaves desmogleins, yielding subcorneal epidermal separation.
- D. Cutaneous streptococcal infections may yield both post-streptococcal glomerulonephritis and scarlet fever, but they do not yield rheumatic fever.

4. C. Staphylococcal scalded skin syndrome (SSSS) is caused by the elaboration of toxins by the bacteria that are distributed systemically, and act to cleave desmogleins in the upper aspects of the epidermis yielding desquamation. Because the toxin is cleared by the kidneys, adults with pre-existing renal insufficiency are at a greater risk for the disease.
5. A. In comparison to ordinary cellulitis, erysipelas is distinguished by brighter (more red) erythema and sharp and well-demarcated lesions. Erysiploid often demonstrates a more dusky and purple erythema. Bilateral lesions are uncommon in both classic cellulitis and erythema and often suggest the existence of a severe exacerbation of stasis dermatitis.
6. B. *Corynebacterium*, like *Corynebacterium minutissimum* that is involved in erythrasma, produced water-soluble coproporphyrin III, which fluoresces a "coral-red" color when examined using a Wood's lamp. Care must be taken not to test recently washed skin, as this may remove the coproporphyrin resulting in a "false-negative" test.
7. A. The ancient name of "malignant pustulosis" to describe cutaneous anthrax is somewhat of a misnomer as lesions of cutaneous anthrax are rarely purulent. With the exception of potential bioterrorism using a "weaponized" strain, most cases of cutaneous anthrax represent an acquired zoonosis and are not fatal. "Edema factor," a toxin elaborated by the organism, can cause significant localized, regional, and even systemic edema.
8. E. Necrotizing fasciitis is a medical emergency. The infection can result in a large degree of tissue loss and mortality, particularly when it is not diagnosed

early. Often the first indication is pain out of proportion to physical findings and exceeding that of simple cellulitis. Tissue necrosis and hemorrhagic bullae often follow later. To make the diagnosis a deep incisional biopsy is needed.

9. C. Hot-tub folliculitis is a self-limited condition caused by the gram-negative organism, *Pseudomonas aeruginosa*. It most often occurs on the skin underneath swimwear and is a result of inadequate chlorination. All the other answer choices are gram-positive organisms.
10. Part A: A-5, B-2, C-1, D-3, E-4; Part B: A-1, B-3, C-4, D-5, E-2.

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FUNGAL DISEASE

ALY RAZA

MELISSA A. BOGLE

MARK LAROCCO

SUPERFICIAL MYCOSES

Tinea Versicolor (Fig. 19-1)

- Caused by *Malassezia furfur*; part of the normal flora, but can also act as an opportunistic pathogen
- Clinical: hypo-, hyperpigmented, or erythematous scaly macules on trunk, extremities; occasionally, an inverse form will affect flexural areas of the body
- Diagnosis
 - Wood's lamp: coppery-orange fluorescence
 - Histology: round to oval yeast with septate hyphae in stratum corneum
- Potassium hydroxide (KOH): "spaghetti and meatballs" appearance of hyphae and spores
- Culture: Saboroud dextrose agar (SDA) with olive oil (fatty acids essential for growth)
- Treatment: topical selenium sulfide (2.5%), topical azole and allylamine antifungals, oral ketoconazole, fluconazole, and itraconazole

Tinea Nigra

- *Hortaea werneckii*, formerly known as *Phaeoannellomyces werneckii*
- Clinical: Brown-black, asymptomatic, nonscaly macules on the palms/soles
- Transmitted by traumatic implantation; incubation period is 2–7 weeks
- Histology: periodic acid-Schiff (PAS)-positive septate brown hyphae in stratum corneum, no tissue response
- KOH: branched brown hyphae with light brown septa
- Microscopic: large, dematiaceous hyphae
- Culture: SDA, brown-black colonies
- Treatment: topical keratolytics and antifungals; topical thiabendazole

Piedra

- *Piedraia hortae* (black piedra); *Trichosporon beigelii* (white piedra)

- Clinical:
 - Black piedra (BP): firmly adherent, pigmented hard nodules on scalp hair (most commonly); metallic sound when combing hair, common in areas with tropical climates
 - White piedra (WP): less adherent, light-brown to white nodules in beard, mustache, or pubic hair, common in temperate and semitropical climates
 - Both infections cause hair breakage
- Diagnosis:
 - KOH of hair shaft: BP: hyphae tightly attached to shaft; WP: hyphae loosely attached to hair shaft
 - Histology: BP – well-organized stroma; hyphae aligned regularly in periphery of nodule, WP – less organized; hyphae perpendicular to shaft
 - Culture: *T. beigelii* requires cyclohexamide-free media; wrinkled, creamy white colonies
 - *P. hortae* grows slowly; dark-brown to black colonies with reddish brown pigment on reverse
- Treatment: shaving, topical imidazoles, selenium sulfide, zinc pyrithione, precipitated sulfur in petrolatum, oral terbinafine for BP

CUTANEOUS MYCOSES

- Filamentous fungi, possessing keratinolytic enzymes, that infect superficial keratinized tissue (skin, hair, and nails)
- May be classified as dermatophytoses or dermatomycoses (non-dermatophyte fungi)
- Three genera of dermatophytes (Tables 19-1 and 19-2)
 - *Trichophyton*: affects hair, nails, skin (Table 19-3)
 - *Epidermophyton*: affects nails, skin
 - *Microsporum*: affects hair, skin
- Different species may show marked host preferences
- Humans (anthropophilic species)
- Animals (zoophilic species; Table 19-4)
- Soil (geophilic species)



FIGURE 19-1 Tinea versicolor. (Courtesy of Dr. Asra Ali.)

Tinea Capitis

- Endothrix infection (growth and sporulation within hair shaft) (Fig. 19-2 and Table 19-5)
 - *Trichophyton tonsurans*: common isolate in the United States causes “black dot” presentation (weak hair shafts break at the skin surface). The clinical presentation may vary from minimal inflammation to diffuse scaling (Fig. 19-3)
 - *T. violaceum*: more common in Europe, North Africa, and Middle East, South Asia
 - *T. schoenleinii*: see below: tinea favosa
- Ectothrix infection (growth and sporulation around hair shaft); tend to fluoresce (see Table 19-6)
 - *Microsporum audouinii*: anthropophilic, causes epidemic tinea capitis, previously most common cause of tinea capitis

TABLE 19-1 Key Morphologic Criteria for Identifying the Dermatophytes

Microscopic Morphology	<i>Epidermophyton</i>	<i>Microsporum</i>	<i>Trichophyton</i>
Macroconidia	Abundant, club-shaped, thick-walled, smooth, arranged in groups	Usually abundant, spindle-shaped, thick-walled, rough	Usually scarce, club-shaped, smooth, thin-walled
Microconidia	Absent	Usually scarce, elongate	Abundant, spherical, elongate, or pear shaped

TABLE 19-2 Differentiating Characteristics of Dermatophytes

Dermatophyte	Colony	Microscopic	Characteristics
<i>T. rubrum</i>	Fluffy white; red on reverse (no diffusion) (see Fig. 19-6)	Smooth, regular-shaped microconidia; “birds on a wire”; thin walled microconidia	Urease (–) Hair perforation (–)
<i>T. mentagrophyte</i> var. <i>mentagrophytes</i> (zoophilic)	Tan, granular, brown-red color on reverse	Grapelike clusters of microconidia and spiral hyphae (see Fig. 19-7)	Urease (+) Hair perforation (+) (+) Hair invasion: large spore ectothrix
<i>T. mentagrophyte</i> var. <i>interdigitale</i>	Cream fluffy; reverse yellow/brown	Few pyriform microconidia	(+) Hair invasion, large spore ectothrix; (+) Hair penetration, urease positive
<i>M. gypseum</i> (geophilic)	Cinnamon, flat powdery with brown reverse color	Thin walled rough macroconidia, less than 6 septa, cucumber-z shaped	(+) Hair invasion: large spore ectothrix, hair fluorescence: none or dull green

(Continued)

TABLE 19-2 (Continued)

Dermatophyte	Colony	Microscopic	Characteristics
<i>M. canis</i>	White fluffy to yellowish with radiating edge, reverse yellow	Rough, canoe-shaped macroconidia; pointed tip ("snout") with at least 6 septa Note: <i>Epidermophyton</i> are smooth-walled	Grows on polished rice (+) hair invasion" small spore ectothrix; green fluorescence
<i>M. audouinii</i>	Downy beige; salmon pink on reverse	Micro- and macroconidia rarely present	Does not grow on polished rice (+) Hair invasion: small spore ectothrix (yellow/green)
<i>T. tonsurans</i>	Brown, yellow, white suedelike; reddish brown on reverse	Smooth balloon-shaped macroconidia (rare); teardrop-shaped microconidia with varying sizes and arrangement	(+) Hair invasion, requires thiamin
<i>T. schoenleinii</i>	Cream-colored, cerebriform, (glaborous), heaped	Antler-shaped hyphae (favic chandeliers)	(+) Hair invasion: fluorescence green causes scutula
<i>T. verrucosum</i>	Cream wrinkled, heaped; cream color on reverse	Smooth-walled macroconidia (rare) with "tails"	(+) Hair invasion: large spore ectothrix, requires thiamin and/or inositol
<i>T. violaceum</i>	Glaborous, wrinkled; reverse violet red	Micro- and macroconidia not present	(+) Hair invasion: endothrix, requires thiamine
<i>T. concentricum</i>	White glaborous; white color reverse	Micro- and macroconidia not present; narrow branching hyphae	Causes tinea imbricata: "tokelau"
<i>E. floccosum</i>	Flat, granular, khaki color front and reverse	Large, thin club-shaped macroconidia	Produces chlamydoconidia
<i>M. nanum</i>	Tan granular; beige color reverse	Rough-walled two-celled macroconidia ("pig snout")	(+) Hair invasion, large spore ectothrix, no fluorescence

TABLE 19-3 Nutritional Requirements of *Tricophyton* Species

Nutritional Requirement	Species
Thiamine	<i>T. tonsurans</i> , <i>T. violaceum</i> , <i>T. verrucosum</i> , some <i>T. concentricum</i>
Histidine	<i>T. megninii</i>
Niacin	<i>T. equinum</i>
Inositol and thiamine	<i>T. verrucosum</i>

TABLE 19-4 Zoophilic Dermatophytes

Dermatophyte	Natural Hosts
<i>M. gallinae</i>	Chickens/other birds
<i>M. nanum</i>	Pigs (snouts)
<i>M. canis</i>	Cats, dogs, horses
<i>T. verrucosum</i>	Cattle, sheep, horses
<i>T. equinum</i>	Horses
<i>T. simii</i>	Monkeys, chickens
<i>T. mentagrophytes</i> var. <i>mentagrophytes</i>	Cats, dogs, rabbits

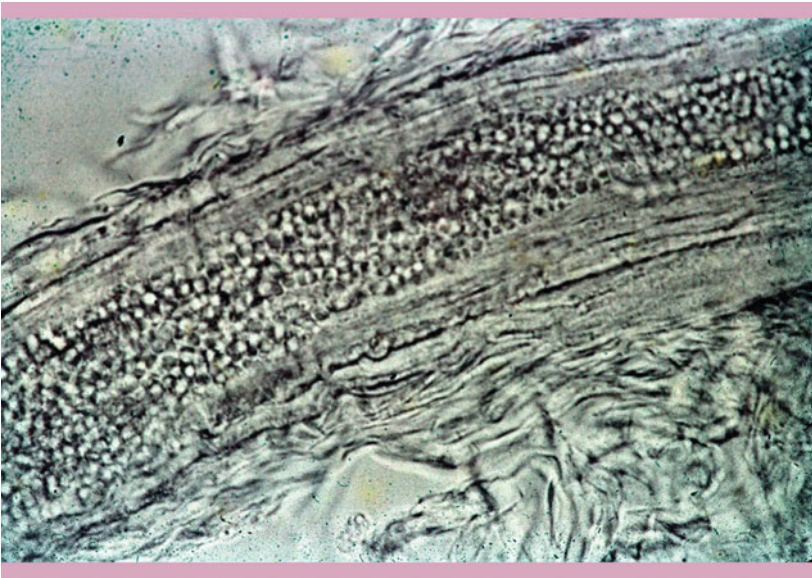


FIGURE 19-2 Endothrix. (Courtesy of Dr. Mark LaRocco.)

TABLE 19-5 Endothrix Fungi

<i>T. tonsurans</i>
<i>T. schoenleinii</i>
<i>T. soudanese</i>
<i>T. gourvilli</i>
<i>T. yaoundie</i>
<i>T. violaceum</i>

- *M. canis*: zoophilic, can cause localized outbreaks, may be acquired from dogs and cats
- *T. mentagrophytes*: zoophilic

Tinea Favosa (Favus)

- Caused by *T. schoenleinii*; less commonly *T. violaceum* and *M. gypseum*
- Favus: formation of air spaces between hyphae within the infected hair
- Clinical: patients present with scutula: yellow crusting that surrounds the hair shaft; later stages result in permanent loss of hair and scarring
- Diagnosis: microscopic: linear arrangement of hyphae along longitudinal axis of hair shaft, bubbling of KOH through the air spaces between hyphae creating characteristic antler “nail head” shaped hyphae
- Treatment: griseofulvin

Kerion

- Suppurative folliculitis
- Deep boggy red areas characterized by a severe acute inflammatory infiltrate
- Usually caused by *Trichophyton* spp.



FIGURE 19-3 Tinea capitis. (Courtesy of Dr. Jason Miller.)

Tinea Barbae

- Usually seen in animal workers (may be contracted from cattle, dogs)
- Caused by both zoophilic (more commonly) and anthropophilic dermatophytes

TABLE 19-6 Small Spore Ectothrix That Fluoresce

Name	Color
<i>M. distortum</i>	Yellow/green
<i>M. audouinii</i>	Yellow/green
<i>M. canis</i>	Yellow/green
<i>M. ferrugineum</i>	Yellow/green
Note: <i>T. schoenleinii</i> (favic type); causes blue/green fluorescence	

- Most commonly caused by *T. verrucosum*; may also be caused by *T. mentagrophytes* var *granulosum*, *M. canis*, *T. schoenleinii*, and *T. megninii*
- Clinical: inflammatory or kerion-like lesions; superficial or sycosiform type: resembles bacterial folliculitis
- Circinate, spreading type: active, vesiculopustular border with central scaling
- Diagnosis: potassium hydroxide preparation: hyphae with or without arthroconidia
- Treatment: oral antifungals: griseofulvin, terbinafine, itraconazole

Tinea Corporis

- *T. rubrum* (most common cause), *M. canis* (children), *T. mentagrophytes*, and *T. tonsurans* (children with tinea capitis)
- Zoophilic fungi:
 - *T. verrucosum* or *T. mentagrophytes*
 - Causes more inflammatory reactions than anthropophilic fungi
- Clinical: scaly erythematous patches with raised borders and central clearing, resulting in an annular shape; borders are scaly, crusted with papules or vesicles (Fig. 19-4)
- Variants:
 - Tinea imbricata or Tokelau
 - Caused by *T. concentricum*, found in the South Pacific, Southeast Asia, Central and South America
 - Concentric circles and polycyclic or serpiginous scaly plaques
 - Bullous tinea corporis: caused by *T. rubrum*
 - Majocchi's granuloma (Fig. 19-5)
 - Deeper involvement of hair follicles with foreign-body granulomas
 - Erythematous patch with perifollicular pustules and nodules
 - *T. rubrum*, *T. violaceum*, *T. tonsurans*



FIGURE 19-4 Tinea corporis. (Courtesy of Dr. Jason Miller.)



FIGURE 19-5 Majocchi's granuloma. (From Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th Ed. New York: McGraw-Hill; 2005, p. 715.)

- Tinea corporis gladiatorum: dermatophyte infection spread by direct contact between wrestlers; lesions usually found on head, neck and arms
- Tinea incognito: tinea coporis modified by corticosteroid application
- Diagnosis:
 - Histology: hyphae between orthokeratosis and compact hyperkeratosis or parakeratosis; spongiosis, superficial inflammatory infiltrate with neutrophils

- Potassium hydroxide (KOH) (Fig. 19-6) examination of skin scrapings reveal numerous septate branching hyphae
- Treatment: topical azoles, allylamines, and ciclopirox olamine; oral azoles, oral terbinafine

Tinea Cruris

- Commonly due to *Epidermophyton floccosum* (Fig. 19-7) or *T. rubrum* (Fig. 19-8)
- Clinical: erythematous patches with central clearing located in the inguinal creases and medial aspects of the thighs, may extend over buttocks and waist, typically spares the penis and scrotum (versus candidiasis)

- Diagnosis: see tinea corporis above
- Treatment: topical azoles, allylamines, and ciclopirox olamine; oral azoles, oral terbinafine

Tinea Pedis

- Dermatophyte infection that affects soles and interdigital spaces of the feet
- Interdigital type with maceration between the toes (often found between the fourth and fifth digits); commonly due to: *T. rubrum*, *T. mentagrophytes* var. *interdigitale*, and *E. floccosum*
- Chronic hyperkeratotic “moccasin type” (Fig. 19-9): erythema with slight scaling may extend to side of feet, caused by *T. rubrum* (most common cause)

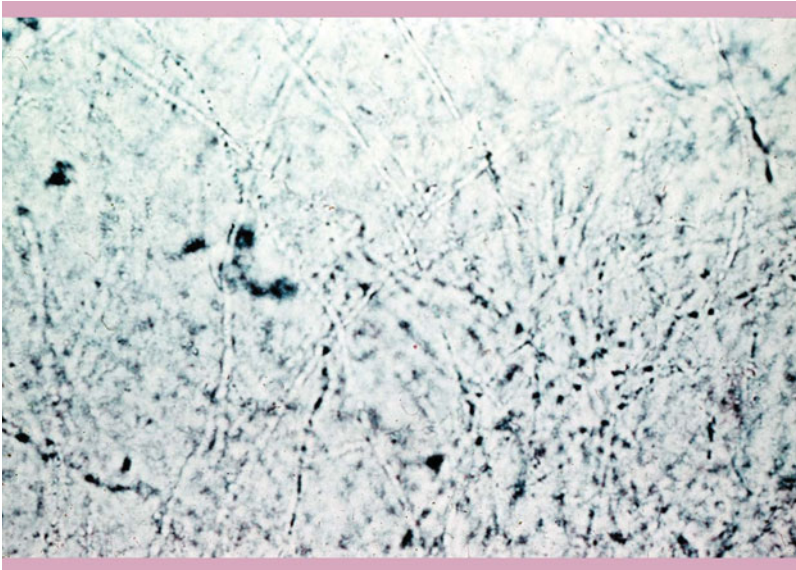


FIGURE 19-6 Potassium hydroxide (KOH) examination of hyphae. (Courtesy of Dr. Mark LaRocco.)



FIGURE 19-7 *Epidermophyton floccosum*. (Courtesy of Dr. Mark LaRocco.)



FIGURE 19-8 *Tinea rubrum*. (Courtesy of Dr. Mark LaRocco.)



FIGURE 19-9 *Tinea pedis*. Chronic hypertrophic. (Courtesy of Dr. Jason Miller.)



FIGURE 19-10 *Tinea pedis*. Vesicular bullous type. (Courtesy of Dr. Asra Ali.)

- Vesicular/bullous type (Fig. 19-10): tender, vesicles or bullae with pruritus; usually seen on the instep or anterior plantar surface of the foot; maybe associated with dermatophytid type reaction (symmetric scaly patches usually found on the hands; thought to be a hypersensitivity reaction to the tinea on the foot, and does not contain fungal elements, caused by *T. mentagrophytes* var. *mentagrophytes* (Fig. 19-11)
- Ulcerative: ulcers and erosions in the web spaces with secondary bacterial infection, usually found in immunocompromised and diabetic patients
- Treatment: keep feet cool and dry, keratolytics with topical antifungals, oral treatment can be used in recalcitrant disease

***Tinea Manuum* (Fig. 19-12)**

- Most commonly caused by *T. rubrum*
- Clinical:
 - Scaly, erythematous patches, pruritic

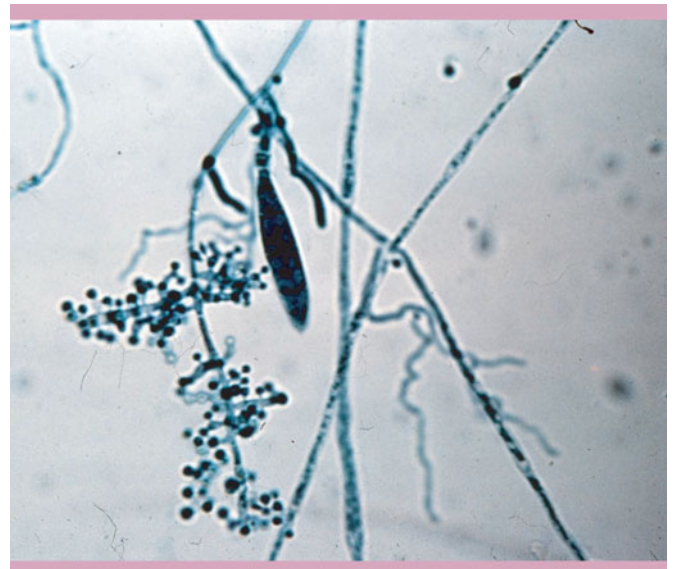


FIGURE 19-11 *Tinea mentagrophytes* var. *mentagrophytes*. (Courtesy of Dr. Mark LaRocco.)



FIGURE 19-12 Tinea manuum. (Courtesy of Dr. Jason Miller.)

- When associated with tinea pedis, may only affect one hand
- Treatment: similar to tinea pedis

Tinea Unguium [Onychomycosis (OM)]

- Fungal infection that affects the toenails or the fingernails
- Main subtypes:
 - Distal lateral subungual OM (DLSO), occurs at free nail edge
 - Thickened nail plate and yellow discoloration, subungual debris, and onycholysis (Fig. 19-13)
 - Most commonly caused by *T. rubrum*
 - Proximal subungual onychomycosis (PSO)
 - Affects proximal nail plate, presents with white discoloration
 - *T. rubrum*, may be associated with HIV
 - White superficial onychomycosis (WSO)
 - Occurs mainly on the toenail surface with white powdery patches on the nail plate, nail is rough
 - *T. mentagrophytes* (adults), *T. rubrum* (children)
 - Endonyx OM (EO)
 - White discoloration of the nail plate, no subungual debris or onycholysis
 - Candidal nail infection: paronychia and/or onycholysis of toenails and/or fingernails; bulbous appearance of digits
 - Most commonly caused by *Candida albicans*
 - Diagnosis: KOH examination, culture, histologic examination of the nail with PAS stain
- Treatment: oral antifungal agents: itraconazole and terbinafine; topical antifungal treatments do not work alone



FIGURE 19-13 Onychomycosis. Distal subungual. (Courtesy of Dr. Asra Ali.)

Id Reaction

- Host's immune response to dermatophytosis
- Occurs at a distant site from the fungal infection
- Lesions are devoid of organisms
- Acute vesicular dermatitis of the hands and feet and evolves into a scaly eczematoid reaction

SUBCUTANEOUS MYCOSES

- Pathogen, involves dermis, subcutaneous tissues, muscle, and fascia
- Mainly occur in the tropics and subtropics; fungi are usually implanted from environmental sources such as plants or soil

Sporotrichosis

- Caused by *Sporothrix schenckii*: dimorphic fungus found on decaying vegetation; infection is acquired by traumatic implantation
- Infection spreads by lymphatic vessels
- Two clinical forms: cutaneous or extracutaneous (pyelonephritis, orchitis, mastitis, synovitis, meningitis, or osseous infection)
- Cutaneous subclassification:
 - Lymphocutaneous form (Fig. 19-14)
 - Nodules with sporotrichoid spread (follows lymphatics) on extremities
 - Fixed cutaneous form: single site (where skin was inoculated), scaly, acneiform, verrucous, or ulcerative nodule; local lymphadenopathy



FIGURE 19-14 Sporotrichosis: Lymphocutaneous form. (From Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th Ed. New York: McGraw-Hill; 2005, p. 739.)

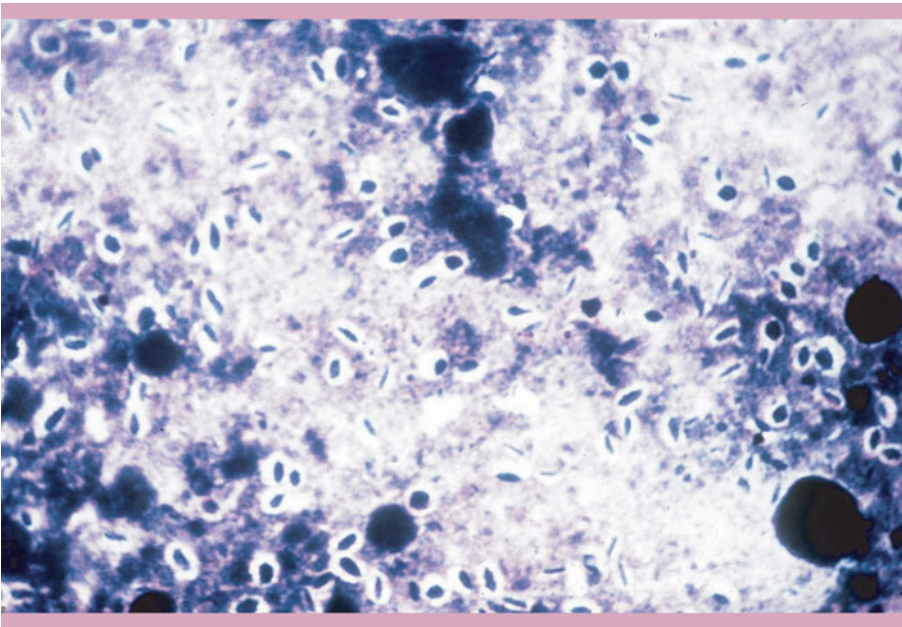


FIGURE 19-15 *Sporothrix schenckii* yeast. (Courtesy of Dr. Mark LaRocco.)

- Other clinical forms: ulcers, or infection associated with draining sinuses
- Pulmonary or disseminated disease: occurs after inhalation with disseminated lesions in joints, lungs, mucous membranes, seen in immunosuppressed individuals
- Diagnosis
 - Histology: asteroid bodies: yeast forms surrounded by refractile eosinophilic halo; yeast forms are sparse and rarely seen, pseudoepitheliomatous hyperplasia with non specific granulomatous inflammation
 - Culture: dimorphic fungus; growth inhibited by cycloheximide
- Yeast phase (37°C) (Fig. 19-15)
 - Consists of elongated, cigar-shaped yeasts; rarely seen in histologic sections of tissue
- Mold/mycelial phase (room temperature; 25°C) (Fig. 19-16)
 - Consists of septate hyphae
 - Turn white to black with age
 - Delicate conidiophores bearing pyriform (pear-shaped) conidia in rosette clusters
- Treatment
 - Lymphocutaneous disease: itraconazole, saturated solution of potassium iodide (SSKI), terbinafine
 - Disseminated or deep infection: IV amphotericin B

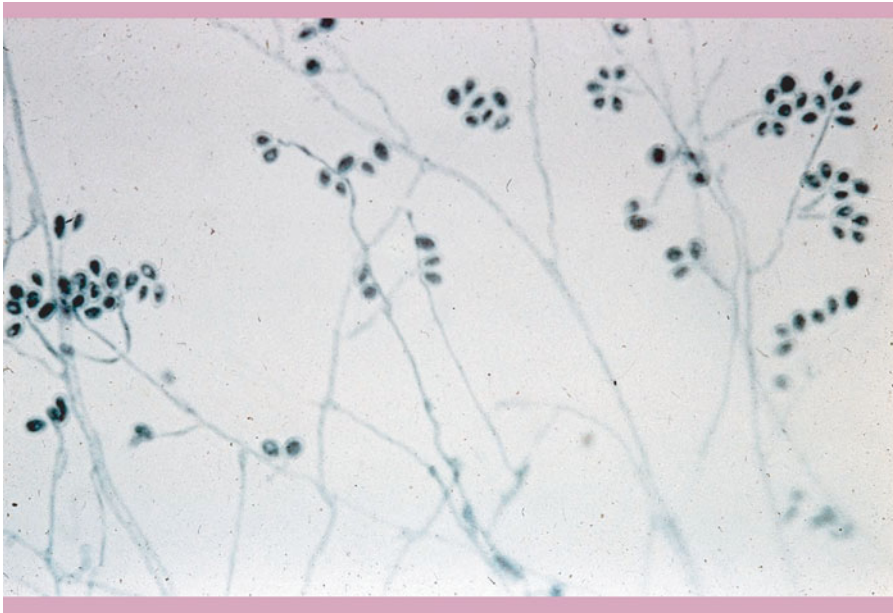


FIGURE 19-16 *S. schenckii* mold.
(Courtesy of Dr. Mark LaRocco.)

Chromoblastomycosis (Chromomycosis, Carrion Mycosis)

- Localized, chronic infection of skin or subcutis by pigmented (dematiaceous) fungi that develop as muriform cells (sclerotic cells or Medlar bodies): small clusters of cells
- Most common agents include *Fonsecaea pedrosii*, *F. compactum*, *Cladophialophora carrionii*, *Rhinocladiella aquaspersa*, *Phialophora verrucosa*, and *Wangiella dermatitidis*
- Acquired by implantation of organisms from soil or decaying wood
- Clinical:
 - Lesions are usually painless, slow growing, verrucous plaques, spread by direct extension; lymphedema may occur locally
 - KOH: brown muriform fungal cells
- Diagnosis:
 - Histology:
 - Pseudoepitheliomatous hyperplasia with inflammatory infiltrate of neutrophils
 - “Sclerotic bodies” (also called *Medlar bodies*, *copper penny bodies*) (Fig. 19-17)
 - Transepidermal elimination of intracellular and clumped organisms with single or double septum
 - Culture: folded gray-green to black colonies
- Treatment: itraconazole, terbinafine, amphotericin B, surgical excision

Subcutaneous Phaeohyphomycosis

- Dematiaceous fungi that cause subcutaneous inflammatory cysts
- Causative organisms: *Exophiala jeanselmei*, *Wangiella dermatitidis*, *Alternaria* spp., *Bipolaris* spp., *Curvularia* spp., *Phialophora* spp

- Clinical: solitary subcutaneous cyst/abscess; may drain
- Diagnosis:
 - Microscopic: branched, septate dematiaceous hyphae
 - Histology: hyphae seen along cyst wall with macrophages
 - Culture: dark leathery or wooly colonies; microscopic evaluation varies with each species
- Treatment: surgery, itraconazole

Mycetoma (Madura Foot, Maduromycosis)

- Includes infections by both actinomycetomas (caused by bacteria) and eumycetomas (caused by fungi)
- Acquired from soil implantation
- Etiologic agents: classification of mycetomas made by examining grains grossly for color and texture (Table 19-7)
- Clinical
 - Lesions involve skin (most commonly on the foot), subcutaneous tissue, fascia, and bone
 - Painless edematous subcutaneous nodules, grow slowly and coalesce. Fistulas and sinus tracts with purulent exudates and extrusion of grains (may infect adjacent tissue), possible bone destruction (Fig. 19-18)
- Diagnosis
 - Culture: etiologic agents are identified according to their microscopic and macroscopic features
 - Serology: ELISA and immunodiffusion
 - Histology:
 - Formation of neutrophil rich granulomas and abscesses that surround filamentous fungal or bacterial grains; size and shape of grains visualized in histopathology may help in their precise identification of eumycetoma or

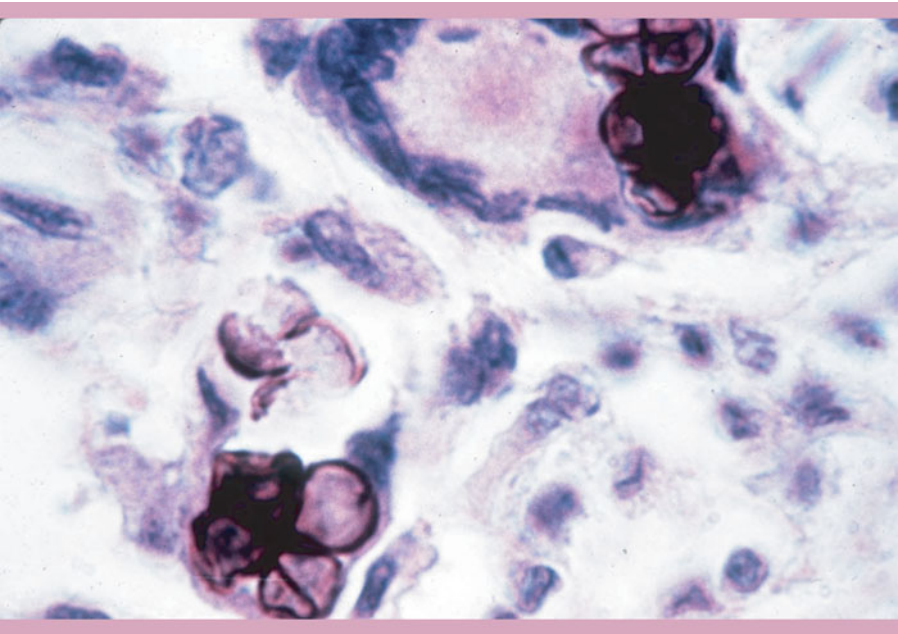


FIGURE 19-17 Chromo blastomycosis. (Courtesy of Dr. Mark LaRocco.)

TABLE 19-7 Identification of *Mycetoma* Microcolonies

Organism	Color of Grain
Eumycetomas	
<i>Madurella mycetomatis</i> (hard)	Dark brown/black
<i>M. grisea</i>	
<i>Leptosphaeria senegalensis</i>	
<i>Pyrenochaeta romeroi</i>	
<i>Scedosporium apiospermum</i>	White/yellow
<i>Acremonium</i> or <i>Fusarium</i> species	
<i>Aspergillus nidulans</i>	
Actinomycetomas	
<i>Actinomadura madurae</i> (soft)	White/yellow
<i>Streptomyces somaliensis</i> (hard)	Yellow
<i>A. pelletieri</i> (hard)	Red
<i>Nocardia brasiliensis</i> (soft)	White/requires direct microscopy to visualize
<i>N. otidiscaviarum</i>	

Hay RJ. Fungal infections. Clin Dermatol. 2006 May-Jun; 24(3):201–212.



FIGURE 19-18 Actinomycetoma. (Courtesy of Dr. Jason Miller.)

actinomycotic mycetoma with fine filaments (Fig. 19-19)

- Treatment: actinomycetomas: combination of sulphamethoxazole-trimethoprim plus rifampin or dapsone and streptomycin. Amikacin or imipenem for recalcitrant *Nocardia* infections
- Eumycetoma: surgical excision

Rhinosporidiosis

- Chronic granulomatous infection caused by *Rhinosporidium seeberi*, controversy over taxonomy of the agent: considered to be an aquatic protozoan (Mesomycetozoa), previously thought to be a fungus
- Endemic in India and Sri Lanka with South America as the second most common source of infection; close contact with rivers and lakes may result in infection

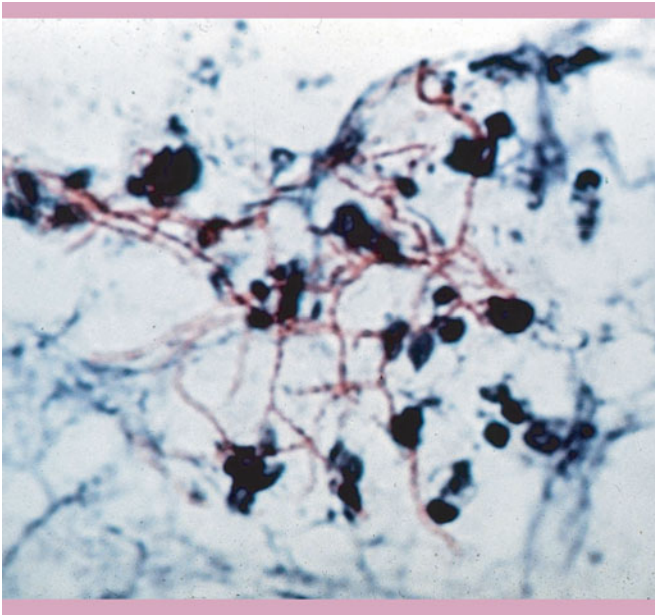


FIGURE 19-19 *Nocardia*. (Courtesy of Dr. Mark LaRocco.)

- Clinical:
 - Intranasal obstructive papules that evolve into large friable pink to deep-red polyps, also affect the nasopharynx
 - Polyps in the lacrimal sac (15%) also can occur: photophobia, redness, and secondary infection
 - Diagnosis:
 - Histology: thick-walled sporangium of 60–450 micrometers containing tens of thousands of sporangiospores
 - Treatment: local surgical excision (recurrence common), adjunctive intralesional amphotericin B
- Lobomycosis (Keloidal Blastomycosis or Lobo's Disease)**
- Caused by *Lacazia loboi* (previously *Loboa loboi*)
 - Zoonosis of freshwater dolphins; found in areas of the Amazon rain forest in South America
 - Clinical: develops at sites of trauma, slow growing keloidal nodules, verrucoid to nodular lesions, crusty plaques, and/or tumors; squamous cell carcinoma may arise in chronic lesions; commonly affects pinna of the ear, and upper and lower extremities
 - Diagnosis:
 - Histology: acanthotic epidermis with parakeratosis, dermal fibrosis with inflammatory infiltrate of giant cells and histiocytes; round shaped organisms (9 nm) joined in a chains; found in macrophage vacuoles
 - Direct microscopy: (samples of tissue), long chains of rounded cells joined by small tubules with a thick cell wall
 - Treatment: surgical excision, clofazamine

DIMORPHIC FUNGI

- See Table 19-8
- Different anamorphic forms or phases
- Regulated by several biologic and physical factors, the most important being temperature
- 25°C fungi grow as molds: soil saprophytes
- 35–37°C fungi grow as yeasts or yeastlike: tissue or parasitic phase
- Disease characteristics
 - Portal of entry: respiratory tract
 - Infection is acquired via inhalation of conidia produced by the mold phase
 - Primary infections occur most commonly in the respiratory tract
 - Can progress to serious pulmonary or disseminated disease with multiorgan involvement
 - Tissue phase not transmissible, no person-to-person spread of infection
 - Extent of disease is regulated by the immunologic response of the host
 - Humoral response
 - ▲ Minimal role in protection
 - △ Sometimes increases disease severity (hypersensitivity responses)
 - △ Measurement of antibody titers is useful occasionally for diagnosis and prognosis (see below)
 - Cell-mediated response (T cells, cytokines, activated macrophages)
 - Primary protective mechanism and major determinant of disease severity

Coccidioidomycosis (San Joaquin Valley Fever, Desert Rheumatism)

- Dimorphic fungi with saprophytic and parasitic phases
- Hosts: humans, dogs, horses
- Acquired by inhalation of arthroconidia of *Coccidioides* spp.
- Lower Sonoran desert, southwestern United States, a soil inhabitant

TABLE 19-8 List of Dimorphic Fungi

<i>Coccidioides immitis</i>
<i>Histoplasma capsulatum</i> and <i>H. duboisii</i>
<i>Blastomyces dermatitidis</i>
<i>Paracoccidioides brasiliensis</i>
<i>Sporothrix schenckii</i>
<i>Penicillium marneffei</i>

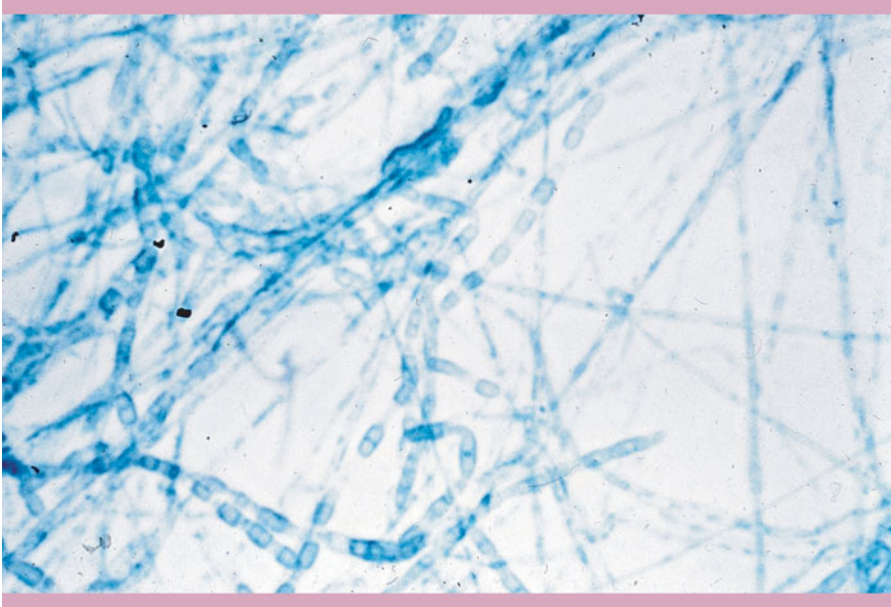


FIGURE 19-20 *Coccidioides immitis* mold phase. (Courtesy of Dr. Mark LaRocco.)

- *Coccidioides immitis* (commonly found in the San Joaquin Valley, California)
- *C. posadasii* (commonly found in southwest United States, Mexico, and South America)
- Clinical:
 - Lungs are usually the primary focus of the infection with subsequent dissemination to skin, meninges, bones and joints
 - Extrapulmonary disease is rare (< 5% of cases) but serious; usually involves central nervous system, skin, and pericardium
 - Up to 60% of cases may be asymptomatic
 - Another 35% present as mild flulike illness with fever, chest pain, and arthralgia
 - Increased risk of infection in immunosuppressed patients, Mexicans, blacks, pregnant women, and Filipinos
- Cutaneous disease
 - Lesions may be organism specific (organisms are identified in skin biopsy and result mainly from hematogenous spread) or a reactive response to the organisms (no viable organisms present)
 - Reactive lesions often present early and include: erythema nodosum, erythema multiforme, Sweet's syndrome, acute generalized exanthem, interstitial granulomatous dermatitis
 - Organism specific lesions include: single or multiple papules, nodules, verrucous plaques, abscesses, pustules, sinus tracts, and/or ulceration
- Diagnosis:
 - Histology: pseudocarcinomatous hyperplasia, dermal and/or subcutaneous inflammation with eosinophils
 - Serology: qualitative and quantitative techniques

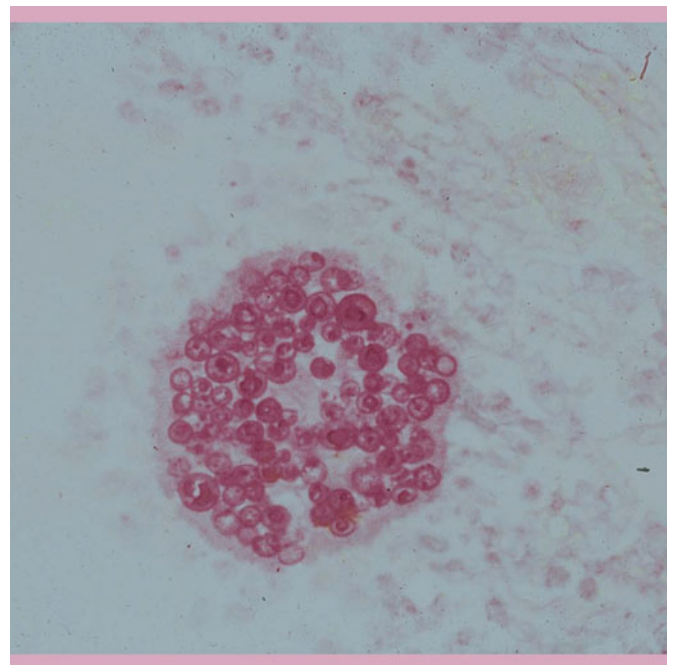


FIGURE 19-21 *Coccidioides immitis* tissue. (Courtesy of Dr. Mark LaRocco.)

- Mycology
 - Mold phase (culture of tissue specimens)
 - ▲ Culture: white to tan fluffy colony matures in 5–10 days
 - ▲ Microscopic: hyphae separate to form barrel-shaped arthroconidia (infectious, may cause lab-acquired disease), (Fig. 19-20) arthroconidia are very
 - Tissue phase (tissue specimen or cytologic smear)

- ▲ Microscopic: multinucleated spherules filled with endospores (produced by repeated cleavage) (Fig. 19-21)
- Chest radiograph: eggshell pulmonary cavities, pneumonia, pulmonary nodules, hilar or mediastinal lymphadenopathy, pleural effusions
- Treatment: not needed for asymptomatic pulmonary disease; extrapulmonary disease and immunosuppressed patients: itraconazole, fluconazole, amphotericin B

Histoplasmosis (Darling's Disease)

- *H. capsulatum* var. *capsulatum* and *H. capsulatum* var. *duboisii* are pathogenic to humans
- Associated with soil containing bird and bat droppings; the organism is most commonly found in Central and North America; in the United States, it is endemic in the Mississippi and Ohio River valleys
- Clinical:
 - Infection begins after inhalation of microconidia – acute pulmonary: self limited illness, fever, chills, dry cough, pneumonia; 5% develop rheumatologic or dermatologic symptoms (erythema multiforme and erythema nodosum)
 - Chronic cavitary pulmonary histoplasmosis: fungal infection is sometimes adjacent to emphysematous bullae with necrosis and increasing fibrosis causing large persistent cavities
 - Disseminated histoplasmosis: develops in immunosuppressed patients: including treatment induced immunosuppression with tumor necrosis factor inhibitors
 - Patients present with fever, malaise, anorexia, and weight loss. On exam: hepatosplenomegaly, lymphadenopathy, pallor and petechiae (with pancytopenia). Cutaneous lesions: mucous membrane ulcerations, skin ulcers, nodules, or molluscum-like papules. If both adrenal glands are severely affected by the infection, Addison's disease can occur
 - Endocarditis and vascular infection: rare manifestation
 - Central nervous system infection: most commonly presents with chronic meningitis
 - African histoplasmosis
 - *H. duboisii*
 - Involves mucocutaneous, bone, lymph nodes, lungs
 - Skin lesions can resemble molluscum contagiosum
- Diagnosis:
 - Mycology
 - Mold (mycelial) phase



FIGURE 19-22 *Histoplasma* colony. (Courtesy of Dr. Mark LaRocco.)

- ▲ Culture: (incubation at 25°) white cottony colony after 2–4 weeks of incubation (Fig. 19-22)
 - ▲ Microscopic: septate hyphae, formation of microconidia (infectious) and tuberculated macroconidia (diagnostic) (Fig. 19-23)
- Tissue phase
 - ▲ Parasitized histiocytes: small (4–6 µm), oval yeasts, usually found in monocytes and macrophages of the blood, lungs, and reticuloendothelial system (Fig. 19-24)
- Laboratory studies: elevated alkaline phosphatase levels, C-reactive protein levels, lactate dehydrogenase levels, and ferritin; pancytopenia
- Histology: oval, narrow-based budding yeast with methenamine silver or periodic acid-Schiff stains; yeasts are usually found within macrophages
- Treatment: none needed for asymptomatic, benign pulmonary disease in immunocompetent patients
 - Moderate disease: itraconazole, fluconazole (second line)
 - Extrapulmonary/disseminated infection in immunocompromised host: amphotericin B

Blastomycosis (Gilchrist's Disease)

- Caused by *Blastomyces dermatitidis*, infections occurs through inhalation of the conidia of the mold form
- Endemic in the Mississippi River valley, southeastern United States
- Clinical:
 - Pulmonary disease occurs, but extrapulmonary presentation is more common with chronic infection of the skin and bones

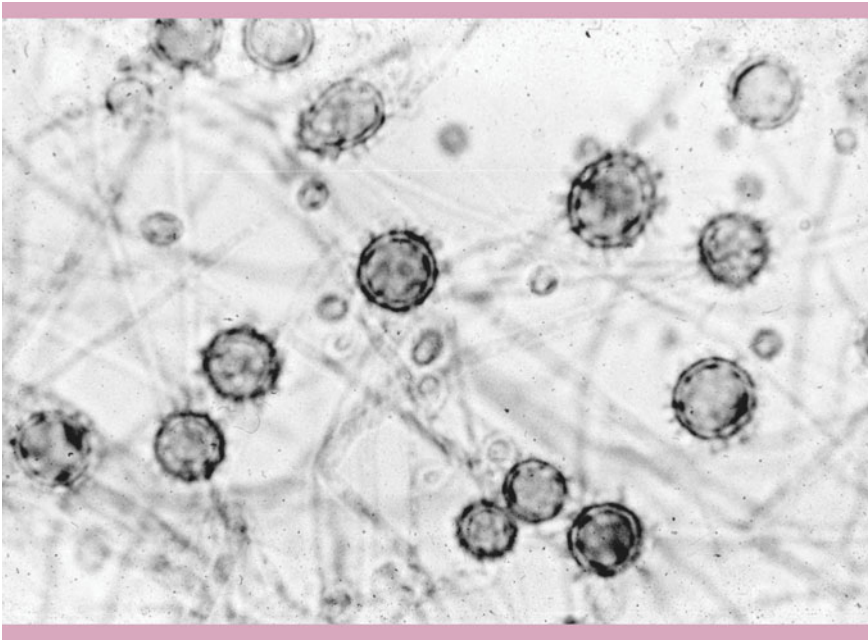


FIGURE 19-23 *Histoplasmosis capsulatum*, mold phase. (Courtesy of Dr. Mark LaRocco.)

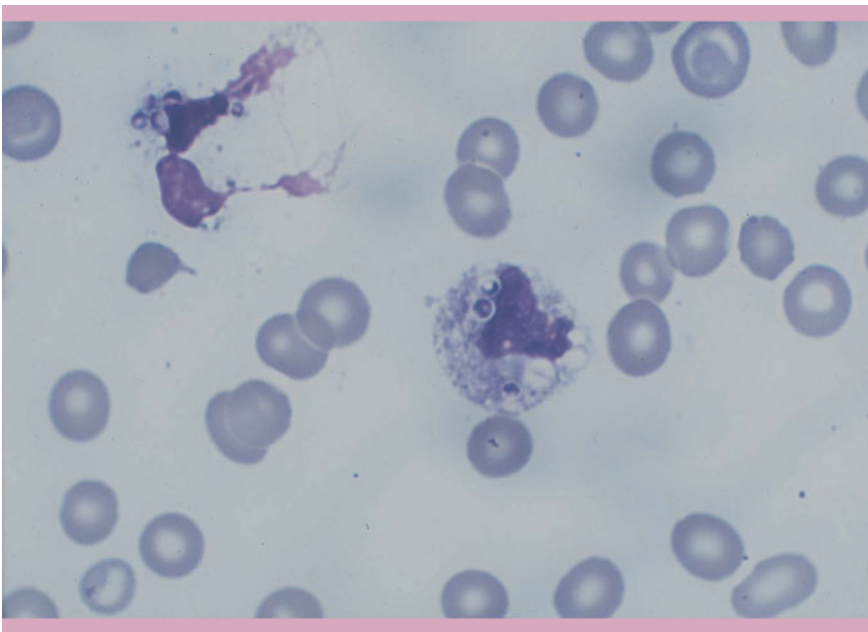


FIGURE 19-24 *Histoplasmosis capsulatum*, yeast phase within histiocytes in peripheral blood. (Courtesy of Dr. Mark LaRocco.)

- Cutaneous lesions:
 - Characterized by microabscess formation, papulopustular well circumscribed nodules, and crusty verrucous granulomas of the hands, face and mucocutaneous areas, cribriform scars
- Other manifestations: genitourinary tract infection, septic arthritis, osteomyelitis
- Systemic blastomycosis
 - Pulmonary spread to skin, bones (osteolytic lesions), genitourinary tract, and CNS
 - Pulmonary disease is similar to tuberculosis
- Inoculation blastomycosis is a rare and mild form of cutaneous disease in lab workers
- Diagnosis:
 - Mycology
 - Mold/mycelial phase
 - ▲ Septate hyphae, white colony in 3–4 weeks
 - ▲ Formation of oval microconidia
 - Tissue phase
 - ▲ Large, thick-walled yeast with broad-based bud (Fig. 19-25)
- Treatment: itraconazole, amphotericin B

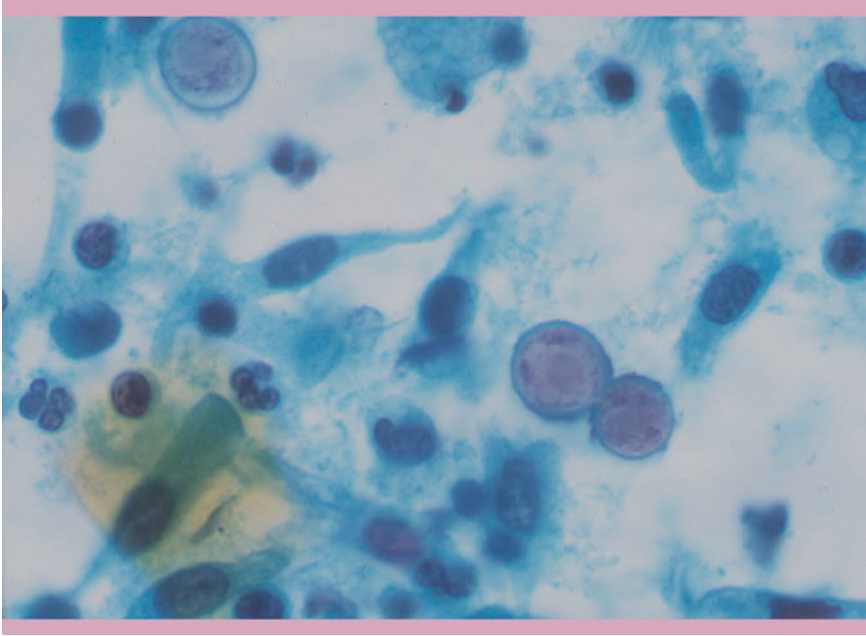


FIGURE 19-25 *Blastomyces dermatitidis*, yeast phase in tissue. (Courtesy of Dr. Mark LaRocco.)

Paracoccidioidomycosis (South American Blastomycosis)

- Caused by *Paracoccidioides brasiliensis*, thermally dimorphic; commonly found in South and Central America
- Chronic, insidious, granulomatous disease
- Clinical:
 - Begins as a pulmonary infection following inhalation of the fungi and then disseminates; patients with lung infection have a productive cough and fever
 - Forms ulcerative granulomata and mulberry-like erosions of buccal (Aguiar-Pupo stomatitis), nasal, and occasionally the gastrointestinal mucosa
 - Lymph node involvement (commonly cervical) with extension to cutaneous tissue
 - Systemic involvement of multiple organ systems is a rare complication: adrenal glands, long bones
 - Male-to-female ratio 8:1 (estrogen may inhibit the hyphae to yeast transformation)
- Diagnosis:
 - Mycology
 - Mold phase (25°C)
 - ▲ Culture: white to tan colony, growth in 2–4 weeks
 - ▲ Microscopic: septate hyphae, oval microconidia indistinguishable from *Blastomyces dermatitidis* (must observe tissue phase)
 - Tissue phase (37°C)
 - ▲ Thin-walled yeast with narrow points of attachment of buds to mother cells “ship’s wheel” configuration; (Fig. 19-26)

- Treatment: itraconazole, ketoconazole, amphotericin B, sulfonamides (sulfamethoxypyridazine and sulfadimethoxine)

SYSTEMIC MYCOSES

- Invade deep structures and spread through hematogenous route to other areas of the body (skin, and mucosa)
- Two forms exist: opportunistic and endemic respiratory mycoses

Systemic Opportunistic Mycoses

CANDIDIASIS

- Candidal infection that result in a heterogeneous group of infectious diseases including systemic, mucocutaneous, and vulvovaginal infections; risk factors for developing candidal infection (Table 19-9)
- *Candida* are unicellular yeasts with thin walled ovoid cells (3- to 6- μ m) that reproduce by budding; they frequently exist as normal inhabitants in the oropharynx, skin, mucous membranes, lower respiratory tract, gastrointestinal, and genitourinary tracts
- Fifteen species exist as significant human pathogens:
 - *Candida albicans* (most common)
 - Examples of non *C. albicans* *Candida* spp.
 - *C. glabrata* (increasing in frequency), *C. tropicalis*, *C. parapsilosis*, *C. krusei*
- Infection is usually of endogenous origin and may occur when: 1) there is increased fungal burden or colonization, 2) there is a breakdown

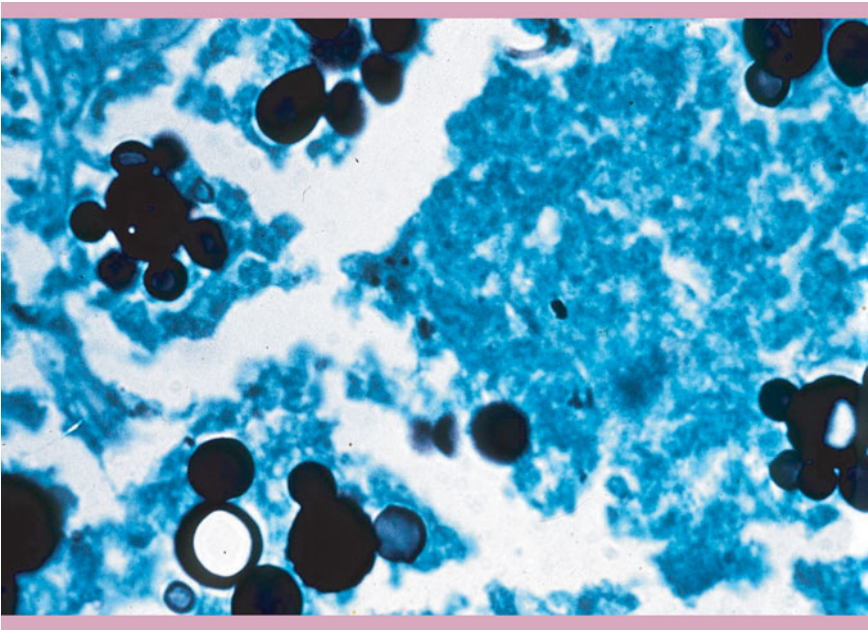


FIGURE 19-26 *Paracoccidioides brasiliensis*, yeast phase in tissue. (Courtesy of Dr. Mark LaRocco.)

TABLE 19-9 Risk Factors for Developing Candidiasis

Adults	Neonates and Children
Prolonged length of stay in an ICU	In addition to the adult risk factors:
High acute physiology and chronic health evaluation	Prematurity
II score (e.g., > 20)	Low Apgar score
Renal failure	Congenital malformations
Hemodialysis	
Broad-spectrum antibiotics	
Central venous catheter	
Parenteral nutrition	
Immunosuppressive drugs	
Cancer and chemotherapy	
Severe acute pancreatitis	
Candida colonization at multiple sites	
Surgery	
Pappas PG. Invasive candidiasis. Infect Dis Clin North Am. 2006 Sep;20(3):485–506.	

- of normal mucosal and skin barriers, 3) immune dysfunction leads to dissemination
- Clinical:
 - Local disease
 - Oral candidiasis (thrush): creamy, white patches on the tongue and oral mucosa, can be

removed by scraping, chronic atrophic disease seen in denture patients with atrophic mucosa, candidal leukoplakia presents with firm, white plaques of the cheeks, lips and tongue, angular cheilitis (perlesche): affects the oral commissures with scale, erythema, and fissures

- Candida esophagitis: seen in immunosuppressed patients (it is an AIDS-defining illness); dysphagia, chest pain, nausea, vomiting
- Vulvovaginal candidiasis: predisposing factors: immunosuppression, antibiotics, contraceptive devices, elevated estrogen; pruritic, erythematous mucosa with thick, white discharge
- Cutaneous candidal infection:
 - Generalized cutaneous candidiasis: presents with diffuse pustular and erythematous eruptions worse in intertriginous areas
 - Erosio interdigitalis blastomycetica: a chronically denuded/macerated area seen in the web space (commonly seen in the third web space of the fingers)
 - *Candida* folliculitis: seen mainly in immunocompromised hosts and among intravenous drug users; pustules and nodules in hair bearing areas
 - *Candida* balanitis: more common in uncircumcised males; infection is acquired with sexual intercourse with an infected partner; burning and itching of the penis with generalized erythema of the glans and/or prepuce, with eroded white papules and white discharge; may spread to buttocks and/or scrotum
 - Intertrigo (Fig. 19-27): occurs in creases and folds of the skin with erosions, oozing, exudation, maceration
 - Candidal paronychia: associated with frequent hand immersion in water and diabetes mellitus, loss of cuticle with erythema and scaling; may present with dystrophic nails
 - Diaper rash (Fig. 19-28): exacerbated by moisture under diapers, erythematous, macerated patches with satellite lesions
 - Perianal candidiasis: skin maceration and pruritus are frequent with frequent extension to the perineum
- Chronic mucocutaneous candidiasis: infections of the skin, mucous membranes, hair, and nails, recalcitrant to treatment; seen in patients with T-cell dysfunction, may be related to autoimmune polyendocrinopathy-candidosis-ectodermal dystrophy (APECED) syndrome
 - Invasive infection (isolation of *Candida* from a normally sterile body site)
- Acute disseminated candidiasis
 - Occurs most commonly among neutropenic patients; erythematous or hemorrhagic palpable rash
- Chronic disseminated candidiasis: seen in neutropenic patients; low-grade fever, right upper quadrant pain, associated with a palpable and tender liver, splenomegaly, and an elevated serum alkaline phosphatase



FIGURE 19-27 Candidiasis. (Courtesy of Dr. Jason Miller.)



FIGURE 19-28 *Candida* diaper. (From Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th Ed. New York: McGraw-Hill; 2005, p. 721.)

- Congenital candidiasis
 - Benign in first 24 hours of life; may have transient respiratory distress; associated with chorioamnionitis
 - Endocarditis: develops mainly in patients with a chronic indwelling catheter, also found in intravenous drug abusers; due to *C. tropicalis* and *C. parapsilosis*

- Vertebral osteomyelitis: usually affects lumbosacral vertebral disks and vertebral bodies; chronic progressive local back pain
- Candida endophthalmitis: retinal lesions associated with untreated candidemia
- Diagnosis:
 - microscopic examination of skin or mucosal scrapings using potassium hydroxide smear or Gram stain
 - 1, 3 b-glucan assay: high sensitivity and specificity
 - Microscopic: pseudohyphae or true septate hyphae (Fig. 19-29)
 - Culture: colonies are white and creamy on Sabouraud dextrose agar after 24–48 hours of incubation at 35°C (Fig. 19-30)
- Treatment
 - Topicals (nystatin, miconazole, clotrimazole) for uncomplicated cutaneous disease
 - Amphotericin B (AMB), liposomal AMB, fluconazole, voriconazole, caspofungin for invasive and/or disseminated disease

CRYPTOCOCCOSIS

- *Cryptococcus neoformans* is the major human pathogen (United States and Europe)
- Four differing serotypes (A–D): *C. neoformans* var *grubii* (serotype A) and *C. neoformans* var *neoformans* *C. neoformans* var *gattii* (serotype B)
- Pigeons are a major reservoir for the fungus
- *C. neoformans* is found in bird droppings
- *C. gatti* (tropics including Africa)
- Found in leaf and bark debris from red gum trees
- Clinical:
 - Respiratory route of entry but primary infection is usually subclinical, can have hematogenous spread to lungs, bones, and viscera
 - Predilection for the central nervous system
 - Skin lesions: widespread papules, acneiform pustules around the nose and mouth, subcutaneous abscesses may ulcerate and form granulomatous, eroded areas, AIDS patients with mollusciform lesions
- Diagnosis:
 - Mycology
 - Slimy mucoid colony on Sabouraud agar at 37°C
 - Encapsulated 4- to 8-µm yeast that produces by single or double buds surrounding clear halo; no pseudohyphae formed (Fig. 19-31)
 - Polysaccharide capsule: serves as a virulence trait of the fungus
 - Stains with mucicarmine; best seen with PAS or GMS
 - India ink smear for CSF

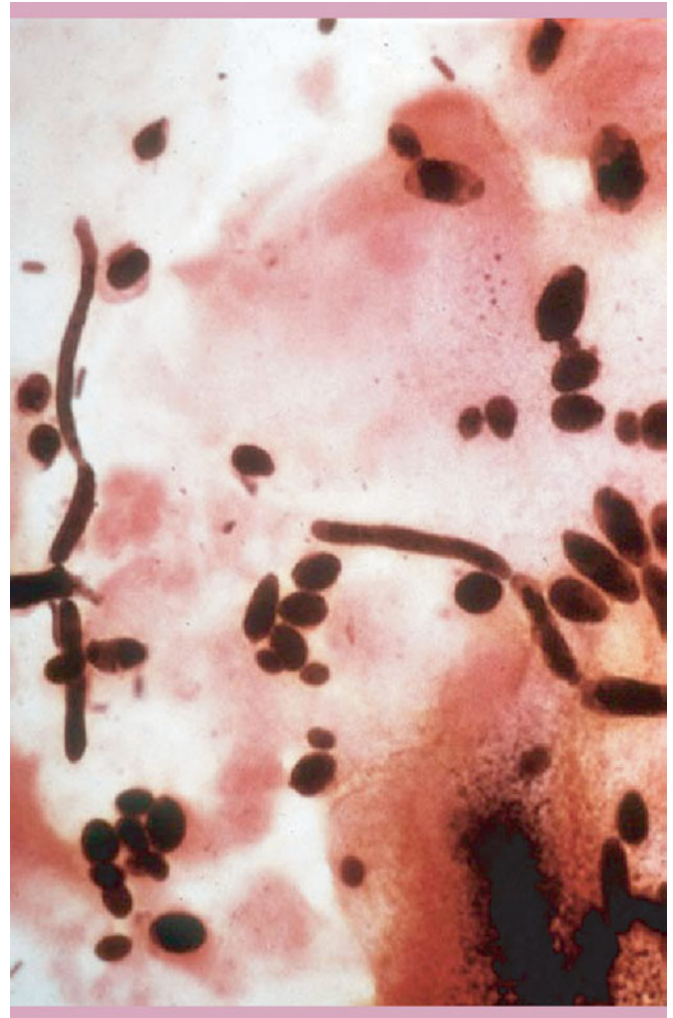


FIGURE 19-29 *Candida albicans*, microscopic view. (Courtesy of Dr. Mark LaRocco.)

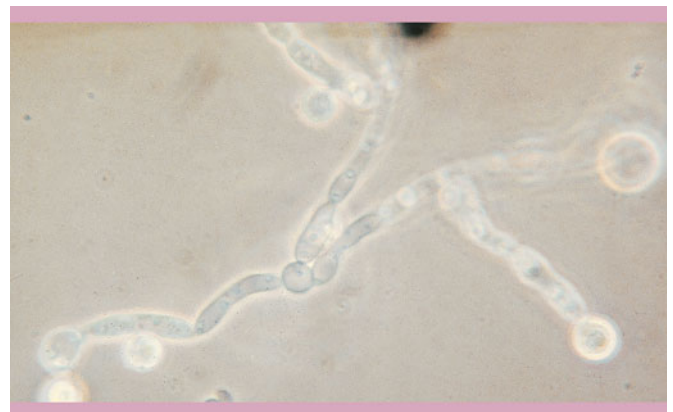


FIGURE 19-30 *Candida albicans* colony. (From Wolff K et al: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th Ed. New York: McGraw-Hill; 2005, p. 717.)

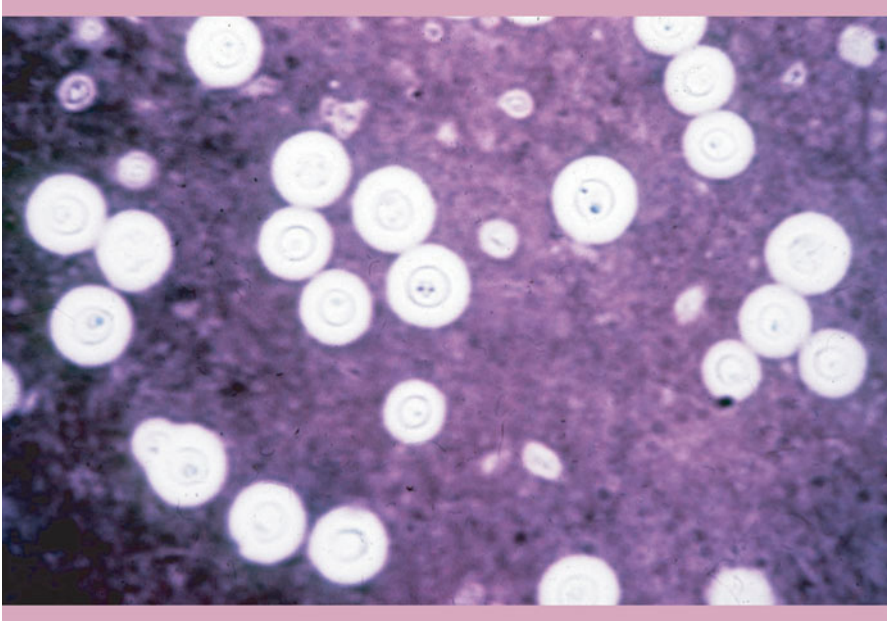


FIGURE 19-31 *Cryptococcus neoformans*, India ink preparation. (Courtesy of Dr. Mark LaRocco.)

- Treatment: amphotericin B, amphotericin B + 5-fluorocytosine, fluconazole

ASPERGILLOSIS

- Ubiquitous mold found in most environments
- *Aspergillus flavus*
 - Most common primary cutaneous pathogen; affects intravenous sites in immunosuppressed patients
- *A. fumigatus*
 - Most common pathogen overall, affecting primarily the lung
- *A. niger*
 - Associated with burn wounds
- Clinical:
 - Infection acquired by inhalation of conidia
 - Allergic bronchopulmonary aspergillosis:
 - Hypersensitivity response to conidiospores; no tissue invasion
 - Aspergilloma (fungus ball); cavities in lungs (tuberculosis, sarcoidosis)
 - Invasive pulmonary aspergillosis
 - Parenchymal invasion with hyphal progression along vascular pathways
 - Disseminated aspergillosis
 - Involvement of two or more non-contiguous organ systems
 - Mycotoxicoses
 - Ingestion of food contaminated with toxins produced by some aspergilli (aflatoxins)
 - Invasive and/or disseminated aspergillosis
 - Often fatal disease in immunosuppressed patients; predisposing factors or conditions

include: neutropenia, neoplasm, organ transplantation, chemotherapy, steroids

- Cutaneous infection: presents as necrotic ulcers or embolic lesions with black eschar
- Diagnosis:
 - Mycology
 - Rapidly growing monomorphic molds
 - Mycelium consists of septate hyaline hyphae
 - Conidiophores with terminal vesicle and phialides produce chains of conidia; different species have different conidial color, size and spatial arrangements (Fig. 19-32)
 - Microscopic examination of tissue
 - GMS, PAS, or calcofluor stains: septate hyphae with 45-degree angle branching (Fig. 19-33)
 - Culture: growth of hyaline mold in 1–2 days on routine fungal media incubated at 25°C. (Fig. 19-34)
 - Conidial pigmentation differs according to species (*A. fumigatus* = green)
 - Serologic tests
 - Antibody tests available for allergic disease and aspergilloma, not good for invasive disease (patients often can't produce antibodies)
 - Galactomannan antigenemia test available; results variable
- Treatment
 - Allergic disease: steroids
 - Aspergilloma: none, surgical resection
 - Invasive disease: amphotericin B, itraconazole, voriconazole, caspofungin

ZYGOMYCOSIS

- Mainly saprophytic fungi

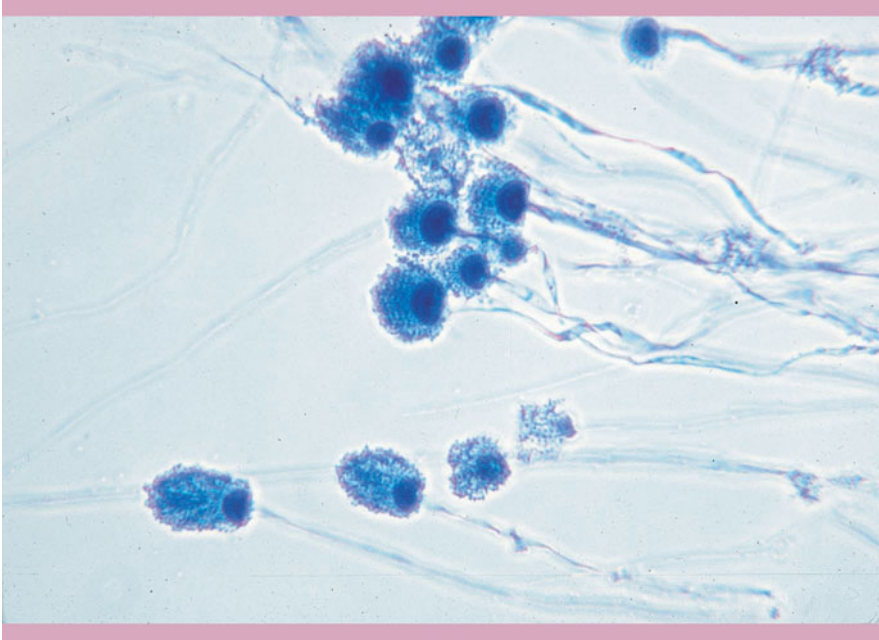


FIGURE 19-32 *Aspergillus*, microscopic view. (Courtesy of Dr. Mark LaRocco.)

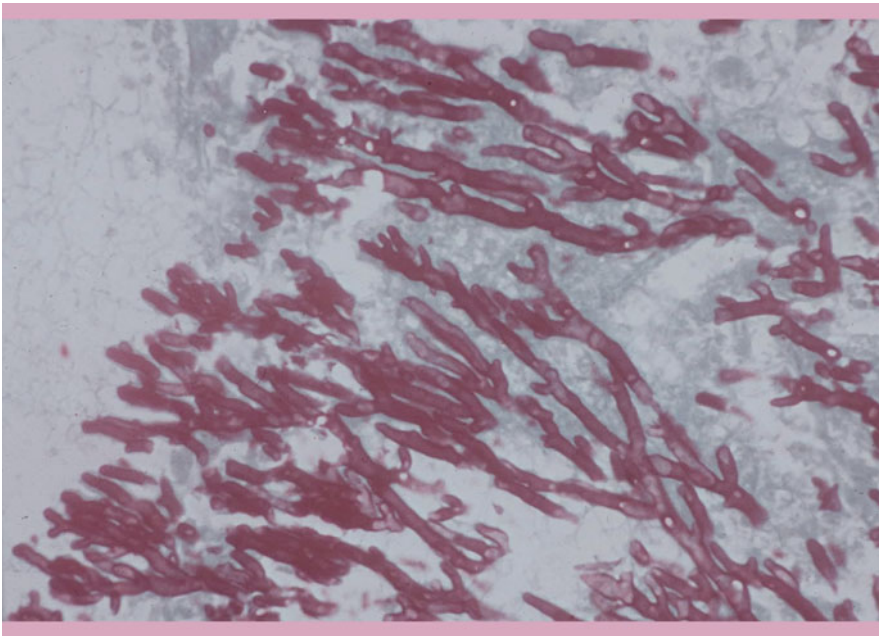


FIGURE 19-33 *Aspergillus* in tissue. (Courtesy of Dr. Mark LaRocco.)

- The medically important orders and genera include:
 - Mucorales, causing subcutaneous and systemic zygomycosis (Mucormycosis) – *Rhizopus*, *Absidia*, *Rhizomucor*, *Mucor*, *Cunninghamella*, *Saksenaea*, *Apophysomyces*, *Cokeromyces* and *Mortierella*
 - Entomophthorales, causing subcutaneous zygomycosis (Entomophthoromycosis) – *Conidiobolus* and *Basidiobolus*
- Order *Mucorales*
 - Clinical presentations
 - Rhinocerebral infection (most common): rapidly progressive infection of sinuses, orbits,

and brain, with infarction and necrosis, associated with ketoacidotic diabetes, sinus pain, proptosis, unilateral palsy, facial edema, purulent drainage, meningitis

- Thoracic infection: pleural disease produces chest pain, cough
- Abdominal, gastric infection: more common in children and malnourished patients
- Skin infection: can affect burn and diabetic patients, local trauma of skin is portal of entry; may present with plaques, pustules, abscesses, or ulceration

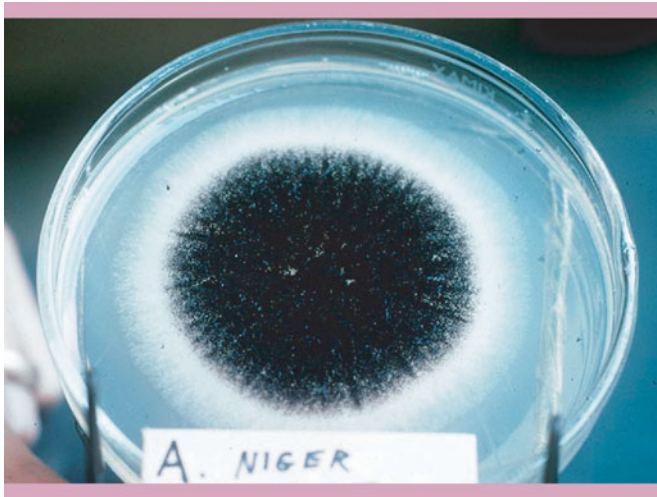


FIGURE 19-34 *Aspergillus* colony. (Courtesy of Dr. Mark LaRocco.)

- Disseminated zygomycosis: occurs in severely debilitated patients
- Central nervous system alone: patients with history of intravenous drug abuse or brain abscess following traumatic implantation
- Order Entomophthorales
 - *B. ranarum* infection presents as a chronic subcutaneous inflammatory or granulomatous disease that affects the limbs, chest, back or buttocks; slowly enlarging hard swelling, on histology: fungal hyphae with eosinophilic infiltrate; commonly seen in children
 - *Conidiobolus* infections present with infection that originates unilaterally in the nasal submucosa with polyp formation
 - Diagnosis:
 - Mycology: white cottony mold, rapid growth (1–2 days) at 25°C on standard fungal media; colony turns dark on sporulation
 - ▲ Microscopic: hyphae are hyaline broad, ribbon-like, and nonseptate; branch at 90-degree angle, asexual reproduction by production of sporangia and sporangiospores
 - ▲ Differentiation of *Rhizopus*, *Absidia*, and *Mucor*-based on the presence of rhizoids and their spatial relation to sporangia
 - △ *Rhizopus*: rhizoids directly opposite sporangia
 - △ *Absidia*: rhizoids between two sporangia (internodal)
 - △ *Mucor*: no rhizoids present
 - Serology: none available
 - Treatment: lipid preparations of amphotericin B (some efficacy, mortality still high), for

Basidobolus infections: oral treatment with potassium iodide, ketoconazole or itraconazole

PENICILLIOSIS

- *Penicillium marneffei*; endemic in Southeast Asia
 - Thermally dimorphic fungus; infection occurs after inhalation of conidia
 - Clinical
 - Fever, weight loss, hepatomegaly, umbilicated papules (molluscum-like) with occasional necrosis- occurs on upper half of the body including the oral mucosa
 - Prominent lymphadenopathy, localized pulmonary lesions in disseminated disease
 - Diagnosis:
 - Mycology
 - ▲ Histology: histiocytes with intracellular yeastlike cells divided by a septum
 - Culture: green or gray mold with diffusible apricot red pigment
 - ▲ Microscopic: hyphae have paintbrush or broom look
 - Treatment: itraconazole, amphotericin B

FUSARIUM

- Common in soil and dead or living plants
- Most common of these are *Fusarium solani*, *F. oxysporum*, and *F. chlamydosporum*
- Immunocompromised hosts, particularly in neutropenic and transplant patients
- Clinical:
 - Infection begins after trauma
 - Can present as central venous catheter infections, septic arthritis, disseminated infections, keratitis, endophthalmitis, endocarditis, peritonitis and fungemia
 - Cutaneous infections include: onychomycosis (superficial white onychomycosis, proximal subungual onychomycosis, and distal and lateral subungual presentation), tinea pedis, localised abscesses or disseminated lesions following hematogenous dissemination (widespread annular lesions often with a central dark or even haemorrhagic area), infection of burn wounds
 - Neutropenic or burn patients are at high risk for infection
- Diagnosis:
 - Culture: colonies are usually fast growing, pale or brightly colored (depending on the species), and may or may not have a cottony aerial mycelium
 - Microscopic: sickle-shaped “banana” multiseptated macroconidia
- Treatment:
 - Very drug-resistant fungi

- Intrinsically resistant to the novel glucan synthesis inhibitors, caspofungin, anidulafungin, and micafungin; can try amphotericin B, voriconazole, and natamycin

OTHER

Protothecosis

- *Prototheca wickerhamii*
- Achloric algae in stagnant, brackish water; spherical unicellular organisms ranging from 3 to 30 μm in diameter
- Ubiquitous in nature; may infect humans through contact with potential sources, such as contaminated soil or water
- Low virulence; risk factor is cellular deficiency
- Clinical
 - Cutaneous lesions: most common site of infection, ill-defined plaque or nodule that may have a verrucous surface
 - Olecranon bursitis
 - Disseminated or systemic infections: in severely immunocompromised patients, organs most commonly affected in dissemination are the skin, subcutaneous tissue, gut, peritoneum, blood, and spleen
- Diagnosis
 - Histology: “morula”; sporangia with a central rounded endospore surrounded by a corona of molded endospores
 - Culture: creamy yeast-like colonies at 30°C, inhibited by cycloheximide
- Treatment: medical and surgical approaches; ketoconazole, itraconazole, fluconazole, conventional amphotericin B, and liposomal amphotericin B

- A. The organism grows in soil in wet or humid climate with rainfall throughout the year
- B. Spherule present (PAS)
- C. Complement fixing antibodies are developed in the early phase of the disease
- D. The organism is *Histoplasma capsulatum*

- Small black nodules up to one mm in size developed along the hair shaft of the scalp. The colonies were brown to black in color. Which of the following is true?
 - A. The etiologic agent is *Piedraia hortae*
 - B. The etiologic agent is *Phaeoannelomysis werneckii*
 - C. The disease is found in temperate climates
 - D. The etiologic agent also causes tinea versicolor
- The organism is a thermally dimorphic fungus. Microscopic examination of the culture grown at 25°C demonstrated septate branching hyphae-bearing rosette-like clusters of conidia. What is your diagnosis?
 - A. Histoplasmosis
 - B. Sporotrichosis
 - C. Coccidioidomycosis
 - D. Cryptococcosis
- Which of the following is true about *Trichophyton tonsurans*?
 - A. The organism is zoophilic
 - B. The organism causes ectothrix infection
 - C. The organism grows best if thiamine is present
 - D. Commonly causes scutula
- A slimy, mucoid colony was grown on Sabouraud agar at 37°C. Budding yeast cells with distinct capsules were observed on microscopic examination. What is this organism?
 - A. *Candida tropicalis*
 - B. *Cryptococcus neoformans*
 - C. *Candida glabrata*
 - D. *Histoplasma capsulatum*

QUIZ

Questions

- On Sabouraud medium at 25°C, tuberculate macroconidia developed. The organism is thermally dimorphic. Which of the following is true?
 - A. The disease is transmitted from person to person
 - B. The organism is *Histoplasma capsulatum*
 - C. The organism is *Blastomyces dermatidis*
 - D. The organism is *Trichophyton rubrum*
- On microscopic examination septate hyphae with barrel-shaped arthroconidia are seen. The fungus is dimorphic. Which of the following is true?
 - A. The organism grows in soil in wet or humid climate with rainfall throughout the year
 - B. Spherule present (PAS)
 - C. Complement fixing antibodies are developed in the early phase of the disease
 - D. The organism is *Histoplasma capsulatum*
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 - A. *Candida tropicalis*
 - B. *Cryptococcus neoformans*
 - C. *Candida glabrata*
 - D. *Histoplasma capsulatum*
- A lactophenol preparation of a dermatophyte revealed grape-like clusters of microconidia. Which of the following is true about this fungus?
 - A. This is *Trichophyton rubrum*
 - B. The organism is anthropophilic
 - C. It is urease positive
 - D. This is *Trichophyton tonsurans*
- The colony is fluffy, white to yellow. Microscopic examination revealed thick-walled macroconidia with more than six septa. Which of the following is true?

- A. The organism is *Micrococcus canis*
 - B. The organism is *Micrococcus audouinii*
 - C. It causes endocarditis infection
 - D. It causes scutula
9. The colony was white fluffy with red pigment on reverse. The microscopic morphology showed smooth peg-shaped conidia. Which of the following is true?
 - A. This is *Trichophyton mentagrophyte*
 - B. This is *Trichophyton rubrum*
 - C. It is usually associated with tinea capitis
 - D. This is *Epidermophyton floccosum*
 10. This bullous type tinea pedis is generally associated with a dermatophyte. Which of the following is true?
 - A. *Trichophyton mentagrophytes* is usually associated with this type of tinea pedis
 - B. *Trichophyton rubrum* is usually associated with this type of tinea pedis
 - C. This is the most common form of tinea pedis
 - D. *Trichophyton tonsurans* is associated with this type of tinea pedis
 11. A PAS shows histiocytes filled with yeasts. On Sabouraud medium at 25°C, a slow-growing white fungus colony developed. What is your diagnosis?
 - A. Coccidioidomycosis
 - B. Blastomycosis
 - C. Histoplasmosis
 12. Microscopic examination from a dimorphic fungus colony revealed large thick-walled yeast with broad-based bud. What is your diagnosis?
 - A. Sporotrichosis
 - B. Coccidioidomycosis
 - C. Blastomycosis
- and immunodiffusion test are positive in 90% of cases in early phase of the disease. The CF is very useful and is last to become positive.
 3. A. Black piedra is a hair disease of the tropics, caused by *Piedraia hortae*. The disease is also known as phaeohyphomycosis. Phaeohyphomycosis is a new concept and include diseases caused by dematiaceous fungi – sclerotic bodies are not present. Sclerotic bodies (“copper penny”) are associated with chromoblastomycosis.
 4. B. These are microscopic features of *Sporothrix schenckii*. Conidiophores bear rosette-like clusters of small round or pyriform conidia. Sporotrichosis is caused by thermally dimorphic fungus. At 37°C, oval, round or fusiform budding cells are produced. The fusiform cells are also called “cigar-shaped bodies.”
 5. C. The most frequently isolated colony of *T. tonsurans* shows flat growth initially, becomes folded with a suede-like surface. The organism is anthropophilic and is a common cause of tinea capitis in the United States and northern Europe. The infection is endocarditis and Wood’s light is not useful. The organism grows best if thiamine is included.
 6. B. This is mucoid colony of *Cryptococcus neoformans* on Sabouraud agar at 37°C. India ink preparation shows yeast cell surrounded by large capsule prepared from culture or spinal fluid.
 7. C. The colony is woolly or silky white (*T. mentagrophytes* var. *interdigitale*) to powdery form (*T. mentagrophytes* var. *mentagrophytes*). Globose (round microconidia in grape-like clusters and sometimes spiral hyphae are noted. The macroconidia when present have thin walls. *T. rubrum* is urease negative and most strains of *T. mentagrophytes* are urease positive.
 8. A. The colony of *Micrascus canis* is woolly white to yellowish in color. The macroconidia are produced in abundance. They have thick walls with six or more septa. It causes ectothrix infection.
 9. B. *T. rubrum* produces peg-shaped microconidia that are uniform in size. Occasionally thin-walled pencil-shaped macroconidia are produced. *T. rubrum* is the major etiological agent of tinea pedis and onychomycosis.
 10. A. Vesiculobullous type tinea pedis is most often caused by *T. mentagrophytes*. The eruptions occur typically with vesicle and bullae in clusters. This form is often responsible for the production of id reaction on the hands. During primary infection a brisk T-cell response develops, which produces and allergic reaction to the fungus.
 11. C. In histoplasmosis, yeasts appear in the cytoplasm of histiocytes and giant cells as numerous

Answers

1. B. *Histoplasma capsulatum* produces tuberculate macroconidia when grown at 25°C. The disease is acquired by inhalation of microconidia and is not transmitted from person to person.
2. B. Hyphae of mycelial forms of *Coccidioides immitis* fragments into arthroconidia with alternating empty spaces. Once inhaled arthroconidia undergo dimorphism and are transformed into spherules containing endospores. The lower Sonoran life zone is ideal for the growth of *C. immitis*; the fungus flourishes in hot, dry environment with minimal rainfall and alkaline soil. The skin test is a useful diagnostic tool. Latex particle agglutination

small spherical or oval-shaped yeast form (1 to 5 μm in diameter).

12. C. Blastomyces dermatidis (a yeast form). In tissue, the fungus forms large, round, budding yeast cells, characterized by thick cell walls and broadly attached daughter yeast cells. The fungus is thermally dimorphic.

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NUTRITION-RELATED DISEASES

CLARE PIPKIN
ASRA ALI

VITAMIN DEFICIENCIES

Vitamin B₃ (Niacin/Nicotinic Acid) Deficiency

- Deficiency results in clinical findings of pellagra from the Italian “pelle agra” for “rough skin”
- Niacin, a B vitamins, can be synthesized from a precursor molecule, tryptophan
 - Deficiency may either be from a niacin or tryptophan deficiency
 - Two coenzyme forms of niacin: nicotinamide adenine dinucleotide (NAD) and NAD phosphate which participate in a variety of redox reactions
- Found in animal proteins, bran, peanuts, legumes, seeds
- Risk factors for development of pellagra
 - Primary (inadequate intake): poverty, restrictive diets, prolonged intravenous supplementation, untreated maize
 - Secondary (inadequate absorption or conversion):
 - Crohn’s disease, GI surgery, intestinal parasites, chronic alcoholism
 - Medications: 6-mercaptopurine, sulfapyradine, 5-fluorouracil, phenobarbitol, ethionamide, pyrazinamide, hydantoins, isoniazid therapy (pyridoxine deficiency secondary to isoniazid treatment could cause pellagra because pyridoxine is required for the conversion of tryptophan to niacin)
 - Carcinoid syndrome: tryptophan diverted to serotonin
 - Hartnup disease: inborn error (autosomal recessive) of tryptophan metabolism
 - HIV
- Clinical
 - Classically described as three Ds: (1) dermatitis, (2) dementia, (3) diarrhea
 - Skin

– Four types of dermatitis:

- ▲ Photosensitive eruption: affecting dorsal hands, feet, forearms, legs, malar region, forehead, tip of nose and “V” of neck (referred to as Casal’s necklace)
- ▲ Perineal lesions
- ▲ Thickening and pigmentation over bony prominences
- ▲ Seborrheic-like dermatitis on the face
- Gastrointestinal tract
 - ▲ Glossitis: atrophy of the papillae of the tongue
 - ▲ Acute inflammation of the small intestine and colon
- Neurologic
 - ▲ Deficiency causes patchy demyelination and degeneration of the various affected parts of the nervous system
 - ▲ Depression, anxiety, irritability, poor concentration, tremor, delusions progressing to encephalopathy
- Diagnosis
 - Made in part by response to niacin supplementation
 - Urinary N-methylnicotinamide and 2-pyridone are the best measurement of niacin status
- Treatment: nicotinamide 100 mg PO q6h for several days or until resolution of major acute symptoms, followed by 50 mg PO q8-12h until all skin lesions heal

Vitamin B₂ (Riboflavin) Deficiency

- Isolated deficiency is rare and is usually associated with other vitamin B complex deficiencies
- Riboflavin is needed as a coenzyme for the activity of flavin adenine dinucleotide (FAD)
- Riboflavin found in milk, organ meat, eggs, leafy green vegetables

- Sensitive to UV radiation
- Deficiency may be primary or secondary
 - *Secondary causes:* alcoholic cirrhosis, hypothyroidism, neonatal phototherapy, chlorpromazine, imipramine, doxorubicin, quinacrine use, acute boric acid ingestion, malabsorptive states
- Clinical
 - Oro-oculo-genital syndrome:
 - Genital dermatoses: often earliest manifestation of deficiency: patchy redness with scaling or fine powdery desquamation, chronic cases result in lichenification
 - Oral changes: angular stomatitis
 - Seborrheic-like scaling of nasolabial folds, ears, outer canthi of the eyelids
 - Rarely corneal vascularization and interstitial keratitis
 - Associated findings: anemia, neurologic dysfunction
- Diagnosis: erythrocyte glutathione reductase level
- Treatment: 5–10 mg riboflavin daily by mouth until corrected

Vitamin B₁₂ (Cyanocobalamin) Deficiency

- Needed by all DNA synthesizing cells including those of hematopoietic and nervous system
 - Cyanocobalamin/hydroxocobalamin found in animal products
 - Absorption occurs through binding with gastric intrinsic factor (IF), produced by gastric parietal cells
 - In states of achlorhydria, IF secretion is reduced, leading to cyanocobalamin deficiency
 - Absorption occurs in distal ileum
- Deficiency usually related to poor absorption states
 - Pernicious anemia (defect in IF)
 - Diseases of terminal ileum (Crohn's disease, short bowel syndrome)
- Since body stores are large it takes 3 to 6 years to develop deficiency
- Clinical
 - Cutaneous findings: generalized hyperpigmentation with accentuation in the flexural areas
 - Glossitis
 - Neuropathy: tingling/numbness in extremities, motor disturbances, cognitive changes, and in extreme cases paralysis
 - Megaloblastic anemia
- Diagnosis
 - Serum cobalamin level
 - Test for pernicious anemia by measuring antibodies against IF

- Schilling test: used to test for malabsorptive states
- Treatment—parenteral cyanocobalamin 1000 µg/d IM/SC for 5 days or 1000 µg IM two times per week for 2 weeks, then 1000 µg/wk IM/SC for 5 weeks, then 100 to 1000 µg IM/SC every month

Vitamin C (Ascorbic Acid) Deficiency (Fig. 20-1)

- Clinical deficiency causes scurvy
- Symptoms develop 1 to 3 months after severe or total vitamin C deficiency
- Vitamin C needed for: antioxidant defense, collagen synthesis (cofactor for prolyl hydroxylase), fatty acid metabolism
- Sources of vitamin C: citrus fruits, berries, tomatoes, broccoli, bell pepper
- Usually a primary deficiency: elderly, alcoholics, psychiatric patients on restrictive diets, sailors (historically)
- Clinically presents with four “Hs”
 - *Hemorrhagic signs:* perifollicular hemorrhage, hemarthroses, subperiosteal hemorrhage, hemorrhagic gingivitis, epistaxis
 - *Hyperkeratosis of hair follicles:* leads to corkscrew hairs
 - *Hypochondriasis:* Cortical thinning, which is sometimes described as a “pencil-point cortex,” scorbutic rosary (resulting from abnormalities at the costochondral junction)
 - *Hematologic abnormalities:* anemia



FIGURE 20-1 Vitamin C (ascorbic acid) deficiency. (Reprinted with permission from Wolff, K et al: *Fitzpatrick's Dermatology in General Medicine*, 7th ed. New York: McGraw-Hill; 2008.)

- Other findings: dry eyes and dry mouth, malaise, lethargy, bone pain, myalgia, delayed wound healing depression
- Diagnosis: low serum L ascorbic acid levels, absent urine vitamin C
- Treatment: oral vitamin C, 800 mg/day for adults, 150 mg/day for children

Vitamin B₁ (Thiamine) Deficiency

- Deficiency causes the condition beriberi
- Thiamine functions in body as part of thiamine pyrophosphate in energy metabolism, synthesis of neurotransmitters
- Thiamine is found in yeast, cereals, liver, meat, eggs, vegetables
- Primary deficiency: seen in strict polished-rice diet
- Secondary deficiency: much more common
 - alcohol related liver disease
 - increased depletion: hyperthyroidism, pregnancy, lactation, diarrhea, dialysis, diuretic use
- Clinical findings
 - Cutaneous: edema, glossitis
 - Neurologic
 - Peripheral neuropathy
 - Mental confusion and confabulation (Korsakoff's syndrome)
 - Wernicke's encephalopathy
 - Cardiovascular: congestive heart failure so called "wet" beriberi
 - Other: anorexia, weakness, constipation
- Diagnosis: most practical to assess response to thiamine replacement, whole blood or erythrocyte transketolase activity may be obtained
- Treatment: variable dosing of thiamine based on severity of symptoms

Pyridoxine (Vitamin B₆) Deficiency

- Needed for the production of non-essential amino acids including aspartic acid and niacin and for production of serotonin
- Pyridoxine is found in animal products, whole-grain products, vegetables
- Usually occurs in association with other deficiencies
- Primary deficiency: alcoholics, elderly
- Secondary
 - Medications: cycloserine, hydralazine, isoniazid, D-penicillamine, pyrazinamide
 - Uremia, cirrhosis
- Clinical
 - Cutaneous: seborrhea-like changes around eyes, nose, mouth
 - May cause all findings seen in niacin deficiency since pyridoxine is a cofactor for niacin production; please see pellagra section for more details

- Oral
 - Glossitis
 - Stomatitis
- Neurologic
 - Depression, confusion, abnormal electroencephalogram
 - Seizures
 - Peripheral neuropathy
- Anorexia, nausea, vomiting
- Anemia
- Diagnosis: decreased serum levels of pyridoxine-5-phosphate
- Treatment: supplementation of pyridoxine 20–100 mg/day orally or 100 mg/day parenterally in adults

Vitamin D₃ (Cholecalciferol) Deficiency

- Vitamin D regulates calcium and phosphorus metabolism, influences alkaline phosphatase levels
- Fat soluble vitamin found in butter, eggs, liver
- Vitamin D [cholecalciferol (vitamin D₃), a steroid compound] is formed in the skin under the stimulus of ultraviolet light
- Other source of vitamin D: ergosterol (vitamin D₂), which is contained in fish liver oil or as an irradiated plant steroid
- Synthesis
 - Cholecalciferol (vitamin D₃) is formed in the skin from 5-dihydrotachysterol
 - Undergoes hydroxylation in two steps
 - First step: occurs at position 25 in the liver, producing calcidiol (25-hydroxycholecalciferol), which is the circulating reserve compound
 - Second step: occurs in the kidney at the 1 position, where it undergoes hydroxylation to the active metabolite calcitriol (1,25-dihydroxycholecalciferol), a hormone
 - Calcitriol [1,25(OH)₂ D₃] acts at three known sites:
 - Promotes absorption of calcium and phosphorus from the intestine
 - Increases reabsorption of phosphate in the kidney
 - Acts on bone to release calcium and phosphate
- Groups at risk for deficiency: breast fed newborns, dark skinned individuals, "excessive" use of sun-screens/sun avoidance, malabsorptive states, elderly, institutionalized, hospitalized
- Clinical:
 - Cutaneous: rarely alopecia
 - Bone abnormalities: osteomalacia in adults, rickets in children

- Rickets: characterized by muscular hypotonia, rachitic rosary along chest, bowing of long bones, skull thickening
- Emerging data that deficiency may increase risk for several cancers including breast, colon, prostate

Vitamin A Deficiency (Fig. 20-2)

- Major functions: vision, immunity, maintenance and differentiation of cells, growth
- Fat-soluble vitamin found in animal fats, liver, and milk
- Primary deficiency: common in developing countries
- Secondary deficiency: diseases of fat malabsorption: Crohn's disease, celiac disease, cystic fibrosis, cholestatic liver disease
- Clinical
 - Cutaneous findings
 - Phrynoderma or toad skin: follicular hyperkeratosis, generalized xerosis
 - Ocular findings
 - Night blindness (nyctalopia), xerophthalmia, Bitot's spots (foci of xerosis of conjunctiva), keratomalacia
 - Other: growth failure, mental retardation, increased susceptibility to measles
- Diagnosis: serum vitamin A level
- Treatment: vitamin A with dosing based on severity of ocular involvement

Vitamin K Deficiency

- Vitamin K is an essential lipid-soluble vitamin that plays a vital role in the production of coagulation proteins



FIGURE 20-2 Vitamin A deficiency. (Reprinted with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th ed. New York: McGraw-Hill; 2003, p. 1404.)

- Vitamin K1 found in green leafy vegetables, Vitamin K2 produced by bacteria in the gut
- At risk groups: newborns in the first two weeks of life, fat malabsorption states, certain antibiotics (cephalosporins, etc), liver disease, megadoses of vitamin A or E
- Clinical: secondary to decrease in vitamin K-dependent clotting factors. II, VII, IX, and X
 - Hemorrhage
 - Ecchymosis
 - Purpura
- Diagnosis
 - Elevated serum prothrombin time (PT) and activated partial thromboplastin time (aPTT)
- Treatment: oral or intramuscular phytonadione, risk of anaphylaxis with intravenous form
- Acute crisis: fresh frozen plasma

MINERAL DEFICIENCIES

Zinc Deficiency

- Essential to the normal function of all cells
- Zinc found in nuts, whole grains, green leafy vegetables, shellfish
- Two types: genetic or acquired
 - Hereditary: acrodermatitis enteropathica (AE) (Fig. 20-3)
 - Autosomal recessive most common type
 - Defect in intestinal zinc specific transporter SLC39A4
 - Clinical signs occur 1 to 2 weeks after weaning from breast
 - ▲ Diarrhea, dermatitis with periorificial and acral distribution, alopecia



FIGURE 20-3 Acrodermatitis enteropathica. (Reprinted with permission from Wolff, K et al: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 6th ed. New York: McGraw-Hill; 2009.)

- ▲ Skin lesions may be vesiculobullous
- ▲ Photophobia, conjunctivitis, cheilitis, stomatitis
- ▲ Failure to thrive, short stature
- ▲ Poor wound healing
- Acquired
 - Alcoholics
 - Complication of malabsorption
 - Inflammatory bowel disease, jejunoileal bypass
- Diagnosis: low plasma or hair levels of zinc, low serum alkaline phosphatase level
- Treatment
 - Zinc gluconate or sulfate oral at 1 to 3 mg/kg per day, IV 300 to 1000 µg/kg per day
 - Warm compresses and petrolatum applied to areas of weeping or crusted dermatitis may enhance reepithelialization when used concurrently with zinc replacement

Iron Deficiency

- Multiple functions in the body including a functional group in hemoglobin for oxygen transportation, helps with storage of myoglobin in muscle, present in peroxidase, catalase, and cytochromes
- Iron found in animal products as well as whole grains, legumes
- Hemorrhage is the most common cause of excessive loss of body iron, but it can occur with hemoglobinuria from intravascular hemolysis; malabsorption of iron is relatively uncommon in the absence of small bowel disease
- Clinical
 - Cutaneous koilonychia: spoon-shaped deformity of the fingernails/toenails, glossitis, angular stomatitis, telogen effluvium
 - Gastrointestinal: anorexia, dysphagia, splenomegaly may occur with severe anemia
 - Plummer-Vinson syndrome: iron deficiency with dysphagia from postcricoid esophageal webs
- Diagnosis: low serum iron levels
- Treatment: iron sulfate 325 mg three times a day

Copper Metabolism Defect

- Menkes' kinky hair disease caused by defective copper absorption (ATP7A gene coding for alpha polypeptide, a copper transporting ATPase is defective)
- X-linked recessive
- Symptoms manifest at 2 to 3 months of age
 - Cutaneous: pale skin, often loose and redundant, pudgy cheeks, horizontal eyebrows
 - Hair: pili torti (180 degree twists of hair), segmental shaft narrowing, trichorrhexis nodosa

- Failure to thrive, lethargy, hypotonia, hypothermia, seizures, mental retardation, osseous alteration, anemia
- Biochemical phenotype involves (1) low levels of copper in plasma, liver, and brain because of impaired intestinal absorption, (2) reduced activities of numerous copper-dependent enzymes, and (3) paradoxical accumulation of copper in certain tissues (i.e., duodenum, kidney, spleen, pancreas, skeletal muscle, placenta)
- Diagnosis: low copper and ceruloplasmin; decreased copper in cultured fibroblasts
- Treatment with copper histidine is usually unsuccessful

Folic Acid Deficiency

- Involved in DNA synthesis
- Found in liver, meat, milk, and green leafy vegetables
- Supplementation in pregnant women recommended to prevent neural tube defects
- Primary deficiency: poor nutrition (alcoholism, elderly, restricted diet)
- Secondary causes of deficiency include:
 - Impaired absorption (celiac disease)
 - Increased requirement (pregnancy, etc)
 - Impaired metabolism (antimetabolites such as methotrexate, trimethoprim)
 - Concomitant B₁₂ deficiency
 - Increased destruction by ethanol metabolite superoxide
- Clinical
 - Hyperpigmentation: patchy distribution
 - Glossitis
 - Cheilitis
 - Megaloblastic anemia
- Diagnosis: serum folate, must also rule out associated B₁₂ deficiency
- Treatment: folic acid

Biotin Deficiency

- Essential cofactor for several carboxylases
- Found in liver, egg yolks, also produced by intestinal bacteria
- Deficiency is rare but can occur in patients with short gut or excessive raw egg-white intake (egg whites contain avidin, a biotin antagonist)
- Prolonged use of certain drugs, especially phenytoin, primidone, and carbamazepine; anticonvulsants inhibit biotin transport across the intestinal mucosa
- Two rare inherited syndromes: both may be fatal if therapy not initiated early on
 - Holocarboxylase synthetase deficiency (neonatal type)

- Biotinidase deficiency (infantile type)
- Clinical
 - Cutaneous findings
 - Scaling eczematoid and xerotic lesions on arms, legs, and feet
 - Perioral and genital erosions
 - Cheilosis, waxy pallor to face
 - Alopecia
 - Conjunctivitis
 - Muscle pain
 - Neurologic findings: depression, lethargy, hallucinations, limb paresthesia
- Diagnosis: urine organic acid analysis may be performed
- Treatment:
 - For adults (acquired form) 60 micrograms/day
 - For inherited forms, 10 to 40 mg/day PO/IV/IM; adjust dose depending on severity of deficiency and response to therapy

Essential Fatty Acid Deficiency

- Unsaturated fatty acids that the body cannot synthesize
- Major EFAs are linoleic, linolenic, and arachidonic acids
- Functions include precursors to prostaglandins, reducing fluidity in phospholipids membranes, energy storage, lamellar granule formation
- Deficiency caused by: low-fat diet, severe malabsorption, long-term parenteral nutrition
- Clinical
 - Cutaneous findings
 - Xerotic, leathery skin with underlying erythema
 - Intertriginous erosions
 - Alopecia
 - Increase in transepidermal water loss
 - Systemic features
 - Growth failure, poor wound healing, neurologic damage
- Treatment: essential fatty acid replacement

PROTEIN-ENERGY MALNUTRITION

Marasmus

- Insufficient protein-calorie intake
- From Greek for “wasting”
- Clinical
 - Cutaneous findings
 - Dry, thin, pale skin
 - Ulcerations
 - Lanugo-like hair
 - Hair is thin, grows slowly and falls out readily

- “Monkey facies” due to loss of subcutaneous fat and wrinkled skin
- Treatment: adequate protein-calorie intake, supplement with zinc and linoleic acid

Kwashiorkor

- From Ghana language meaning “sickness of the weanling”
- Insufficient protein intake but with adequate, sometimes excessive carbohydrate consumption
- Often associated with multiple nutritional disorders
- Clinical
 - Cutaneous findings
 - Dyschromia
 - Superficial desquamation in mild cases (“enamel paint spots”), in severe cases large areas of erosion (“flaky paint”)
 - Diffuse erythema that may progress to purpura
 - Hair is sparse, brittle
 - Flag sign bands of light and dark hair relating to periods of malnutrition
 - Nails soft and thin
 - Mucosal lesions, cheilosis, xerophthalmia, vulvovaginitis
 - Systemic features
 - Edema secondary to hypoalbuminemia
 - Anorexia, irritability, apathy
 - Failure to thrive
 - Superimposed bacterial and fungal infections
 - Bilateral parotitis, hepatomegaly, diarrhea, loss of muscle mass
- Treatment: fluid and electrolyte abnormalities and treatment for any infections

OTHER

Hypervitaminosis A

- May occur after single meal of liver of polar bear, bearded seal
- Clinical
 - Cutaneous
 - Loss of hair, coarseness of hair
 - Generalized exfoliation and pigmentation
 - Cheilitis
 - Pruritus
 - Lethargy, anorexia, weight loss
 - Bone fracture, bone pain
- Carotenoderma
 - Results from high intake of beta-carotene (natural provitamin of vitamin A) containing vegetables and fruits
 - Skin is yellow-orange, most prominent in areas of high sebaceous gland density (nasolabial folds, forehead)

- Will disappear when dietary patterns are changed

Iron Excess: Hemochromatosis

- Toxicity owing to excess iron can occur either acutely after a single large dose of iron or chronically owing to excessive accumulation of iron in the body from either diet or blood transfusions or both
- Early symptoms include
 - Severe fatigue
 - Impotence
 - Arthralgia
- Later, patients may experience
 - Skin bronzing or hyperpigmentation
 - Diabetes mellitus
 - Cirrhosis
- Diagnosis:
 - A persistently elevated transferrin saturation in the absence of other causes of iron overload
 - Serum ferritin levels elevated higher than 200 µg/liter in premenopausal women and 300 µg/liter in men and postmenopausal women indicate primary iron overload owing to hemochromatosis
 - Genetic testing for 2HFE gene mutations C282Y and H63D
- Treatment
 - Weekly therapeutic phlebotomy of 500 mL whole blood (equivalent to approximately 200 to 250 mg iron)
 - Deferoxamine mesylate (Desferal): drug of choice used in primary and secondary iron overload syndromes

- A patient who follows a strict polished-rice diet may develop all of the following findings EXCEPT:
 - Glossitis
 - Phrynoderma
 - Congestive heart failure
 - Confusion
 - Neuropathy
- A hunter who eats the liver of a polar bear may develop which of the following findings?
 - Cheilitis
 - Hypertrichosis
 - Genital dermatitis
 - Peripheral neuropathy
 - Anemia
- An infant presents with yellow discoloration of the skin with accentuation in the nasolabial folds but no scleral icterus. Which investigation will lead to the correct diagnosis?
 - Asking about recent diarrhea and weight loss
 - Obtaining serum transaminases and liver ultrasound
 - Asking about protein intake
 - Asking about vegetable intake
 - Asking about calcium intake
- A patient who presents with follicular hyperkeratosis and growth failure should be assessed for all of the following EXCEPT:
 - Cystic fibrosis
 - Crohn's disease
 - Liver disease
 - Pernicious anemia
 - Celiac disease

QUIZ

Questions

- A diet high in untreated corn may result in all of the following findings EXCEPT:
 - Photodistributed eruption
 - Thickening over bony prominences
 - Diarrhea
 - Hemorrhagic signs
 - Glossitis
- This vitamin functions as cofactor for prolyl hydroxylase and is critical to collagen synthesis:
 - Vitamin B₁
 - Vitamin B₂
 - Vitamin C
 - Vitamin D
 - Vitamin K
- A patient who follows a strict polished-rice diet may develop all of the following findings EXCEPT:
 - Glossitis
 - Phrynoderma
 - Congestive heart failure
 - Confusion
 - Neuropathy
- A hunter who eats the liver of a polar bear may develop which of the following findings?
 - Cheilitis
 - Hypertrichosis
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 - Peripheral neuropathy
 - Anemia
- An infant presents with yellow discoloration of the skin with accentuation in the nasolabial folds but no scleral icterus. Which investigation will lead to the correct diagnosis?
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 - Asking about protein intake
 - Asking about vegetable intake
 - Asking about calcium intake
- A patient who presents with follicular hyperkeratosis and growth failure should be assessed for all of the following EXCEPT:
 - Cystic fibrosis
 - Crohn's disease
 - Liver disease
 - Pernicious anemia
 - Celiac disease
- A low serum alkaline phosphatase may be seen in association with:
 - A periorificial rash
 - Anemia
 - Pili tori
 - Generalized hyperpigmentation
 - Peripheral neuropathy
- Koilonychia, or spoon-shaped nail, may be seen most commonly with deficiency of which mineral?
 - Calcium
 - Zinc
 - Iron
 - Magnesium
 - Selenium

9. A diet high in raw egg whites may cause a deficiency of:
 - A. Biotin
 - B. Zinc
 - C. Pyridoxine
 - D. Vitamin C
 - E. Vitamin B₁₂
10. A child presents with significant edema, areas of eroded skin with a flaky paint appearance, and hair with bands of light and dark. Which disorder is he most likely to have?
 - A. Marasmus
 - B. Kwashiorkor
 - C. Essential fatty acid deficiency
 - D. Beri beri
 - E. Scurvy

Answers

1. D. A diet high in untreated corn may result in niacin deficiency. The classic triad is that of dermatitis, dementia, and diarrhea. Hemorrhagic signs may be seen with vitamin C deficiency.
2. C. Vitamin C is a cofactor for prolyl hydroxylase. Deficiency leads to hemorrhagic signs, bony abnormalities, anemia and delayed wound healing.
3. B. A polished-rice diet may lead to a thiamine deficiency. Clinical findings include glossitis, neurologic problems including neuropathy, confusion, encephalopathy, as well as congestive heart failure. Phrynoderma or “toad skin” is associated with vitamin A deficiency.
4. A. The liver of polar bear is very high in vitamin A. A single meal may result in vitamin A toxicity. Findings that may be seen include alopecia, generalized exfoliation, pruritus, cheilitis as well as lethargy and bone pain.
5. D. Carotenoderma results from a high intake of beta-carotene (a natural provitamin of vitamin A) containing vegetables and fruits. The yellow color is often most prominent in areas of high sebaceous gland density. Unlike jaundice from liver disease, there is no scleral icterus.
6. D. Vitamin A is a fat soluble vitamin and deficiency may result from fat malabsorption. All disorders except pernicious anemia may lead to fat malabsorption. Vitamin A deficiency may result in generalized xerosis, follicular hyperkeratosis, ocular findings including night blindness and keratomalacia as well as growth failure. Deficiency has been associated with an increased susceptibility to measles.
7. A. A low serum alkaline phosphatase level is associated with zinc deficiency. Zinc deficiency may manifest with dermatitis in the periorificial and acral distribution, alopecia, photophobia, stomatitis, and failure to thrive.
8. C. Koilonychia is most commonly associated with iron deficiency. Other findings may include glossitis, stomatitis, and anemia.
9. A. Egg whites contain avidin, a biotin antagonist.
10. B. Kwashiorkor develops when there is insufficient protein intake but with adequate, sometimes excessive caloric intake. Edema often occurs secondarily to hypoalbuminemia.

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CUTANEOUS FINDINGS RELATED TO PREGNANCY

RONALD P. RAPINI

COMMON SKIN CHANGES RELATED TO PREGNANCY

- Hyperpigmentation of nipples, external genitalia
- Linea nigra: midline pigmentary demarcation line on abdomen
- Melasma: ill-defined pigmentation of cheeks, forehead
- Striae: start reddish, become whitish, redness may be improved faster by pulsed dye laser, but otherwise that and other treatments unproven to have long-term benefit
- Vascular lesions: varicosities, pyogenic granuloma
- Increased or changing nevi, melanoma: unclear if truly increased over controls
- Telogen effluvium typically starts 3 months after delivery

PRURITUS GRAVIDARUM

- This is itching without rash (up to 14% of all pregnancies)
- Potential intrahepatic cholestasis of pregnancy should be investigated in these patients, but this occurs in only 1–2% of all pregnancies, clinical jaundice in only 0.02% of pregnancies
- Elevated liver function tests and serum bile acid levels may occur
- Elevated glutathione S-transferase alpha (GSTA), a specific marker of hepatocellular integrity, identifies women with intrahepatic cholestasis and distinguishes them from those with benign pruritus gravidarum
- Reported increases in rates of premature delivery and perinatal mortality appear to be restricted to those in whom frank clinical jaundice develops

- Recurs in 50% of pregnancies
- Treatment: phenobarbital, cholestyramine, (ursodeoxycholic acid controversial but advocated by some)

PRURITIC URTICARIAL PAPULES AND PLAQUES OF PREGNANCY (PUPPP), POLYMORPHOUS ERUPTION OF PREGNANCY (PEP) (FIG. 21-1)

- The term PUPPP seems to be preferred in the United States and PEP in Europe
- Polymorphous eruption with papules, plaques, urticarial lesions
- The most common of the pregnancy rashes (0.6% of all pregnancies)
- Onset in abdominal striae is common, then commonly spreads to abdomen, buttocks, thighs
- Spongiosis may occur and cause confusion with pemphigoid gestationis, then immunofluorescence biopsy may be needed, since pemphigoid gestationis possibly may cause increased fetal morbidity or mortality, unlike PUPPP
- Intensely pruritic, like most of these pregnancy rashes
- Primagravids mostly, does not recur with subsequent pregnancies
- Increased incidence of twins, rapid maternal weight gain
- Usually third trimester
- Biopsy not very specific: perivascular lymphocytes with eosinophils, edema, sometimes with spongiosis or parakeratosis



FIGURE 21-1 Pruritic urticarial papules and plaques of pregnancy (PUPPP). Note accentuation of rash in striae. (Courtesy of Dr. Asra Ali.)

PEMPHIGOID GESTATIONIS (HERPES GESTATIONIS) (FIG. 21-2)

- The term pemphigoid gestationis is preferred by many because “herpes gestationis” causes confusion with herpes virus infection and its implications.
- Onset second or third trimester
- Papules, urticarial plaques, vesicles, bullae
- Often develops around umbilicus and extremities, later spreading to trunk, palms, soles. Usually spares face and mucous membranes
- Autoimmune disease similar to bullous pemphigoid (but linear C3 more often seen at dermal-epidermal junction zone than IgG)
- Increased HLA-DR3, DR4
- Circulating IgG1 autoantibodies in the blood are called herpes gestationis factor, avidly fixes complement to basement membrane zone of epidermis (in bullous pemphigoid, IgG4 is dominant over IgG1)
- Target antigen is most often the NC16a domain of 180kDa protein associated with basal keratinocyte



FIGURE 21-2 Pemphigoid gestationis. Papules and vesicles in this case. (Courtesy of Dr. Ronald Rapini.)

hemidesmosomes (collagen XVII, formerly called bullous pemphigoid antigen 2). Bullous pemphigoid patients may have the same target antigen, but almost always have a second target: dystonin (DST), a 230kDa protein formerly designated BP antigen 1. The latter antigen is less commonly found in pemphigoid gestationis

- Maternal health not affected, but there may be increased fetal morbidity, small infant size. Less than 5% of infants have skin lesions, these spontaneously resolve

ATOPIC ERUPTION OF PREGNANCY (NEW TERM FOR PRURIGO GESTATIONIS)

- Often atopic diathesis
- Excoriated papules predominant
- Onset usually in second or third trimester
- No adverse maternal or fetal effects
- A variant known as papular dermatitis of Spangler is probably not a real entity: marked elevation of 24-hour urinary human gonadotropin (hCG) and decreased plasma estriol and cortisol was supposedly associated with fetal complications

PUSTULAR PSORIASIS OF PREGNANCY (IMPETIGO HERPETIFORMIS) (FIG. 21-3)

- Often no previous history of psoriasis
- Rarest of the pregnancy rashes mentioned here
- Papules, scaly plaques, pustules coalescing into lakes of pus
- Favors thighs, groin, trunk, extremities. Spares face, hands, feet
- Constitutional signs: fever, chills, nausea, vomiting, diarrhea, fatigue
- Leukocytosis, secondary hypoalbuminemia, hypocalcemia, tetany
- Often recurs in subsequent pregnancies, menses, oral contraceptives
- Increased morbidity of fetus possibly from placental insufficiency

DISTINGUISHING POINTS

- All of the rashes are most common in third trimester, but pemphigoid gestationis may occur in the second or third, and impetigo herpetiformis may occur in any trimester
- Pemphigoid gestationis is the only one with immunofluorescence findings
- Pemphigoid gestationis is the most likely one to recur in subsequent pregnancies
- The three with supposed increase fetal morbidity-mortality are pemphigoid gestationis, pruritus gravidarum (if cholestasis), and impetigo herpetiformis
- Most of these rashes, regardless of type, tend to resolve after delivery of the baby.

- All are treated with antihistamines (diphenhydramine is the most popular since it is FDA pregnancy class B). Cetirizine, cyproheptadine, and loratadine are also class B. Topical corticosteroids are often used but are class C. Prednisone is reserved for more serious cases, class B later in pregnancy

QUIZ

Questions

- The most common rash of pregnancy is:
 - Pemphigoid gestationis
 - Impetigo herpetiformis
 - Pruritic urticarial papules and plaques of pregnancy (PUPPP)
 - Papular dermatitis of pregnancy
 - Autoimmune progesterone dermatitis
- The eruption most characteristically beginning in the abdominal striae is:
 - Pemphigoid gestationis
 - Impetigo herpetiformis
 - Pruritic urticarial papules and plaques of pregnancy
 - Papular dermatitis of pregnancy
 - Autoimmune progesterone dermatitis
- Prurigo gestationis has been re-named or considered to be in the same group with:
 - Pemphigoid gestationis
 - Atopic eruption of pregnancy
 - Impetigo herpetiformis
 - Pruritus gravidarum
 - Polymorphous eruption of pregnancy
- Increased fetal mortality has been considered a significant feature according to some authorities in all except:
 - Pemphigoid gestationis
 - Impetigo herpetiformis
 - Papular dermatitis of pregnancy of Spangler
 - Pruritus gravidarum with jaundice
 - Pruritic urticarial papules and plaques of pregnancy
- Hypoparathyroidism, hypocalcemia, hypophosphatemia, decreased vitamin D levels, elevated erythrocyte sedimentation rate, and leukocytosis are characteristic features that may occur in:



FIGURE 21-3 Impetigo herpetiformis. Pustules are predominant. (Courtesy of Dr. Asra Ali.)

- A. Pemphigoid gestationis
 - B. Impetigo herpetiformis
 - C. Papular dermatitis of pregnancy
 - D. Pruritus gravidarum
 - E. Pruritic urticarial papules and plaques of pregnancy
6. Match the condition with an important finding:
- | | |
|----------------------------|------------------------------------|
| a. Pemphigoid gestationis | A. Elevated liver function tests |
| b. Pruritus gravidarum | B. Periumbilical accentuation |
| c. PUPPP | C. Psoriasis variant |
| d. Progesterone dermatitis | D. Last trimester in primagravidas |
| e. Impetigo herpetiformis | E. Skin test for diagnosis |
7. The immunoprofile most characteristically found in pemphigoid gestationis is:
- A. Circulating IgG1 autoantibodies, target NC16a domain of 180-kD BPAg2 (type XVII collagen)
 - B. Circulating IgG4 autoantibodies, target 180-kD, BP Ag2
 - C. Circulating mixed IgG autoantibodies, target 180-kD, BPAg2
 - D. Circulating IgG4 autoantibodies, target BPAg1
 - E. Circulating IgG1 autoantibodies, target BPAg1
8. Which of the following pregnancy conditions characteristically does not recur with subsequent pregnancies?
- A. Impetigo herpetiformis
 - B. Pemphigoid gestationis
 - C. Pruritus gravidarum
 - D. Pruritic urticarial papules and plaques of pregnancy

Answers

1. C. PUPPP is the most common pregnancy rash, which is fortunate since it has no known fetal complications. The others which are listed are relatively rare.
2. C. PUPPP often begins in the abdominal striae, and sometimes initially they just look red rather than like a rash. Pemphigoid gestationis often is prominent in the periumbilical area.
3. B. Prurigo gestationis is now often considered to be within the spectrum of disease of the atopic eruption of pregnancy, though this terminology is new and may not be universally accepted. The same British group has long advocated using the term pemphigoid gestationis for herpes gestationis (to avoid confusion with herpes virus) and polymorphous eruption of pregnancy for what we usually call PUPPP in the United States.
4. E. The data for this are not great, as massive epidemiological studies have not been done, but PUPPP is the only one mentioned that has not been associated with increased fetal mortality.
5. B. It is important to watch the calcium level in impetigo herpetiformis. Leukocytosis in these sick patients can be confused with infection, so that blood cultures are sometimes needed if they are febrile.
6. a.B; b.A; c.D; d.E; e.C. Not all itching pregnancy patients have elevated liver function tests, but if they do, we have to worry about cholestasis and increased fetal problems. PUPPP mainly affects first pregnancies and does not usually recur. Progesterone dermatitis is really rare, but is diagnosed by skin test.
7. A. The autoantibodies of pemphigoid gestationis are of the IgG1 subtype, and these strongly fix complement. In bullous pemphigoid, IgG4 is dominant.
8. D. Most of the pregnancy rashes can recur with subsequent pregnancies except PUPPP, which usually affects primagravidas.

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CUTANEOUS MANIFESTATIONS OF RHEUMATOLOGIC DISEASES

ASRA ALI
CAROLYN BANGERT

CONNECTIVE TISSUE DISEASES

- Group of systemic autoimmune diseases
- Screening
 - Antinuclear antibody (ANA): performed using indirect immunofluorescence (IF)
 - Varying concentrations of patient serum is incubated with a tissue substrate (usually human epithelial tumor line HEP-2), and any autoantibodies to nuclear antigens present in the serum bind to the substrate
 - A fluoresceinated antibody is added, and the tissue is observed under fluorescent microscopy to check for a specific staining pattern
 - Results reported as:
 - Titer: level of anti-nuclear antibodies significant enough to be defined as a positive ANA. The standard definition is the titer exceeding that found in 95% of normal individuals (5% of normal individuals can be ANA-positive, with titers usually $\leq 1:320$ and a speckled or homogeneous pattern)
 - Pattern: corresponds to the presence of a specific antibody. A certain pattern may indicate the presence of various rheumatologic diseases
 - A positive ANA is seen in:
 - ▲ Systemic lupus erythematosus (SLE): 99%
 - ▲ Systemic sclerosis (SSc) patients: 97%
 - ▲ Dermatomyositis (DM) patients: 40% to 80%
 - ANA patterns and their corresponding antibodies:
 - Homogeneous pattern (Fig. 22-1): (complete nuclear fluorescence) specific for SLE
 - dsDNA (double-stranded DNA or native DNA): 70% SLE, associated with lupus nephritis
 - Histone: 50% to 70% SLE; also the antibody found in drug-induced SLE (*but not in drug-induced subacute cutaneous lupus*)
 - Rim pattern: (fluorescence at edges of nucleus), anti-DNA, anti-histone and anti-laminin antibodies: SLE (most specific) but also may be seen in chronic active hepatitis
 - Speckled pattern (Fig. 22-2):
 - SS-A/Ro: 30% to 40% SLE; often with SCLE (subacute cutaneous lupus erythematosus), drug-induced SCLE, and neonatal LE; also seen in Sjogren's syndrome (SS), dermatomyositis (DM)
 - SS-B/La: 15% SLE often with SCLE, drug-induced SCLE, neonatal LE
 - Anti-ribonucleoprotein (RNP): 30% SLE; associated with MCTD (mixed connective tissue disease)
 - Anti-Smith (Sm): 20% to 30% SLE; very specific
 - Nucleolar pattern (homogeneous, speckled, or clumpy staining of nucleolus):
 - RNA polymerase I (RNA pol 1): 4% to 23% SSc
 - U3 RNP/fibrillarin: SSc
 - Topoisomerase I (Scl-70): 22% to 40% of SSc, associated with diffuse SSc(Pm-Scl)
 - PM-Scl: SSc-polymyositis overlap
 - Centromere pattern (antibodies to kinetichore proteins):
 - 22% to 36% of SSc patients

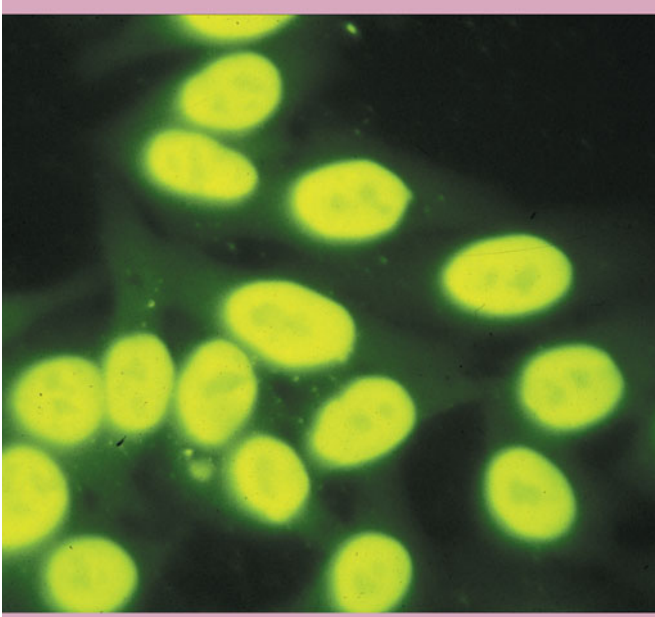


FIGURE 22-1 Homogeneous pattern. (Courtesy of Dr. Robert Jordon.)

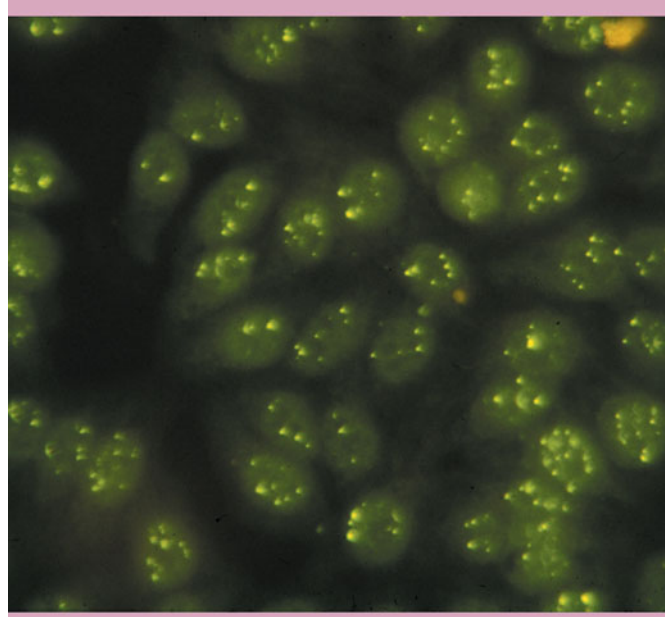


FIGURE 22-2 Speckled pattern. (Courtesy of Dr. Robert Jordon.)

- 60% to 90% of limited SSc patients (e.g., CREST syndrome [calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly, telangiectasias])
- Extractable nuclear antigens (ENAs)
 - Soluble cytoplasmic and nuclear components that are bound by autoantibodies
 - Antibodies include Ro, La, Sm, RNP, Scl-70, Jo-1
 - ENA-4 test:
 - Identifies Ro, La, RNP, and Sm
 - Used to diagnose SLE, MCTD, and SS

Lupus Erythematosus

- Autoimmune disorder with a spectrum of presentations; may be cutaneous and/or systemic
- Cutaneous lupus subsets:
 - Acute cutaneous lupus erythematosus (ACLE)
 - Subacute cutaneous lupus erythematosus (SCLE)
 - Chronic cutaneous lupus erythematosus (CCLE)
 - Systemic lupus erythematosus (SLE)
- Acute cutaneous lupus (ACLE): most specific for SLE (Fig. 22-3)
 - Localized ACLE (malar rash): occurs in 20% to 60% of SLE patients
 - Lasts from days to weeks
 - Violaceous erythematous patches or plaques over the malar eminences, may involve entire face with sparing of the nasolabial folds
 - May heal with dyspigmentation or poikiloderma, but does not scar
 - Often is painful or pruritic



FIGURE 22-3 Acute cutaneous lupus erythematosus. (Courtesy of Dr. Melissa Costner.)

- Associated with sun exposure; systemic disease flaring is common
- Histologic findings: focal liquefactive degeneration of the basal cell layer; perivascular and periadnexal lymphocytes
- Immunohistology (Fig. 22-4): IgG and C3 along dermal-epidermal junction in a continuous

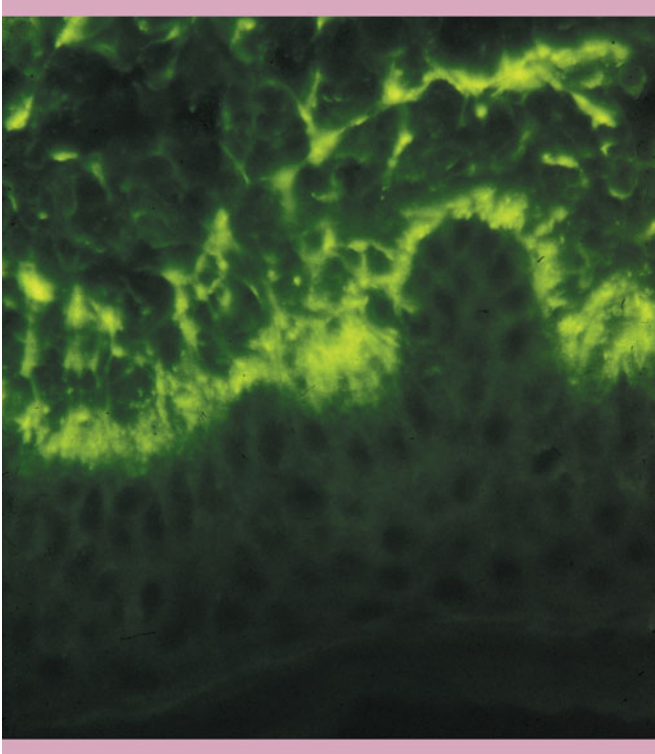


FIGURE 22-4 Immunohistology of systemic lupus erythematosus. (Courtesy of Dr. Robert Jordon.)

granular or linear bandlike array (lupus band: lesional or nonlesional)

- Generalized ACLE: characterized by erythematous macular or papular scaling, with or without edema; crusting and bullae can be present; spares the knuckles when it involves the hands (while dermatomyositis, involves the knuckles)

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

- Multisystem autoimmune disorder
 - Found commonly in women of child bearing age
 - Associated with human leukocyte antigen (HLA): DR-2 and DR-3
 - Diagnostic criteria for SLE (4 of 11 of these criteria must be met for diagnosis)
 - Mucocutaneous
 - Malar rash: see description above
 - Discoid rash (erythematous plaques with adherent keratotic scaling and follicular plugging with atrophic scarring in older lesions)
 - Oral (or nasal) ulcers
 - Photosensitivity: skin rash following exposure to UV-B radiation (ie: sunlight or fluorescent lights)
 - Systemic
 - Arthritis: two or more joints characterized by tenderness, swelling, or effusion; non-erosive
 - Serositis
 - ▲ Pleuritis: history of pleuritic pain or rub heard by physician or evidence of pleural effusion
 - ▲ Pericarditis: documented by electrocardiogram (ECG), rub, or evidence of pericardial effusion
 - Renal involvement: proteinuria, cellular casts in urinalysis, elevated serum creatinine, and decreased albumin levels
 - Hematologic disease: hemolytic anemia with reticulocytosis, leukopenia, lymphopenia, or thrombocytopenia
 - Neurologic disorders: seizures or psychosis, in the absence of offending drugs or known metabolic disorders
 - ANA (anti-nuclear antibody): 95% sensitivity
 - Immunologic disorders: anti-ds DNA, anti-smith antibodies, antiphospholipid antibodies, biologic false positive serologic test for syphilis
- Other associated manifestations of lupus that may be associated with disease flares
 - Constitutional symptoms: fever, malaise, weight changes
 - Leukocytoclastic vasculitis
 - Urticaria, urticarial vasculitis (including hypocomplementemic urticarial vasculitis)
 - Lupus panniculitis (can also occur without SLE)
 - Livedo reticularis: especially in patients with antiphospholipid antibodies
 - Raynaud's phenomenon (20% to 30% of patients)
 - Alopecia: patchy or generalized, nonscarring, similar to telogen effluvium; "lupus hairs" = wispy short hairs at anterior frontal hairline
 - Arthralgias
 - Headache
 - Stroke, transient ischemic attacks (may be related to antiphospholipid antibodies)
 - Myelopathy
 - Abdominal pain: related to peritonitis, mesenteric vasculitis, and/or bowel infarction
 - Libman-sacks endocarditis, accelerated cardiovascular disease with angina
 - History of recurrent spontaneous abortions may indicate the presence of antiphospholipid antibodies
- Laboratory tests
 - Anti-phospholipid antibodies: (anticardiolipin immunoglobulin G or immunoglobulin M, or lupus anticoagulant); associated with livedo reticularis, arterial and venous thrombosis without vasculitis or active SLE, and increased incidence of fetal wastage
 - Anti-dsDNA: high specificity; sensitivity is 70%, levels may correlate with disease activity (particularly with SLE nephritis)

- Anti-Smith: highly specific for SLE, sensitivity is 30% to 40%
- Anti-SSA (Ro) or anti-SSB (La): 15% in SLE patients; associated with neonatal lupus
- Anti-ribosomal P
- Anti-RNP: may be found in patients with mixed connective tissue disease with overlap SLE
- Coomb's test: anemia with antibodies on red blood cells
- Anti-histone: drug-induced lupus erythematosus (DILE)
- Other immunologic changes (not part of the criteria)
 - Complement deficiency: C3, C4, and C1q; low complement levels associated with flaring of systemic disease
- Other diagnostic tests
 - Erythrocyte sedimentation rate (ESR) and or C-reactive protein (CRP): elevation in these markers of inflammation
 - Complete blood count: check for hemolytic anemia with reticulocytosis, leukopenia, lymphopenia, or thrombocytopenia
 - Urinalysis: check for proteinuria, cellular casts
 - Magnetic resonance imaging: evaluate for vasculitis, stroke
 - Computed tomography: assess for pneumonitis
 - Renal biopsy: evaluate presence and type of glomerulonephritis
 - Skin biopsy: dermal-epidermal junction with lymphocytes and vacuolar change at the basal cell layer
- Treatment
 - Prednisone
 - Azathioprine (Imuran)
 - Mycophenolate mofetil (CellCept)
 - Cyclophosphamide (Cytoxan)
 - Hydroxychloroquine (Plaquenil): cutaneous and articular disease, reduces flares of systemic disease
 - Thalidomide: cutaneous disease; do not use with positive antiphospholipid (aPL) antibodies (increases risk of thrombosis)

DRUG-INDUCED LUPUS ERYTHEMATOSUS (DILE)

- Autoantibody profile varies from classic SLE; no renal or CNS involvement; malar and discoid lesions uncommon
- Associated with antihistone antibodies and antinuclear antibodies commonly, not as common: anti-SS, anti-SSA
- Associated with HLA-DR4
- Patients who are slow acetylators have a higher incidence of DILE
- Can appear in up to one-fifth of patients with SLE
- Patients have one or more clinical symptoms of SLE (noninflammatory joint pain [90% of patients])

- Etiologic agents
 - Antiarrhythmics: procainamide and quinidine
 - Antibiotics (minocycline, rifampin, voriconazole)
 - Antitubercular: isoniazid
 - Anti-fungal: griseofulvin
 - Anticonvulsants (valproate, ethosuximide, carbamazepine, phenytoin and hydantoins)
 - Hormonal therapy (leuprolide acetate, oral contraceptives)
 - Antihypertensives (hydralazine, methyldopa, diltiazem and captopril)
 - Anti-inflammatory (D-penicillamine and sulfasalazine)
 - Antipsychotics (chlorpromazine)
 - Cholesterol-lowering agents (lovastatin, simvastatin, and gemfibrozil)
 - Antimalarial: hydroxychloroquine
 - Others: glyburide, gold salts, interferon, amiodarone, docetaxel
- Laboratory tests
 - Positive ANA in 95%
 - Anti-histone antibodies in >75%, homogenous pattern (50% to 70% of patients with classic SLE)
 - Drugs with homogenous pattern: procainamide, isoniazid, timolol, hydralazine, and phenytoin
 - In contrast, drug-induced subacute cutaneous lupus has a speckled pattern (anti-SSA/Ro), associated with thiazide diuretics, terbinafine
 - Complement levels normal
 - Treatment: not needed; symptoms usually clear within weeks of stopping the implicated drug

SUBACUTE CUTANEOUS LUPUS ERYTHEMATOSUS (SCLE)

- Associated with HLA-B8, HLA-DR3, HLA-DRw52, and HLA-DQ1
- Usually occurs in Caucasian females; seen in 9% to 27% of patients with SLE
- Clinical (Fig. 22-5)
 - Begins as erythematous papules or plaques
 - Annular lesions or scaling plaques (psoriasiform or lichenoid), usually on sun-exposed areas of the body but can be generalized
 - Knuckles are usually spared when lesions occur on the hands (rash of dermatomyositis typically involves the knuckles)
 - photosensitivity to UVB, UVA, and rarely visible light
 - Waxing and waning course; may heal with transient hypopigmentation or even permanent leukoderma
- 50% of patients meet the ACR criteria for SLE, (most commonly: arthritis, leukopenia, positive ANA, and photosensitivity)
- Only 10% to 20% of patients develop severe SLE (e.g., nephritis, CNS disease)
- Drug-induced SCLE: most commonly hydrochlorothiazide, calcium channel blockers, angiotensin-converting

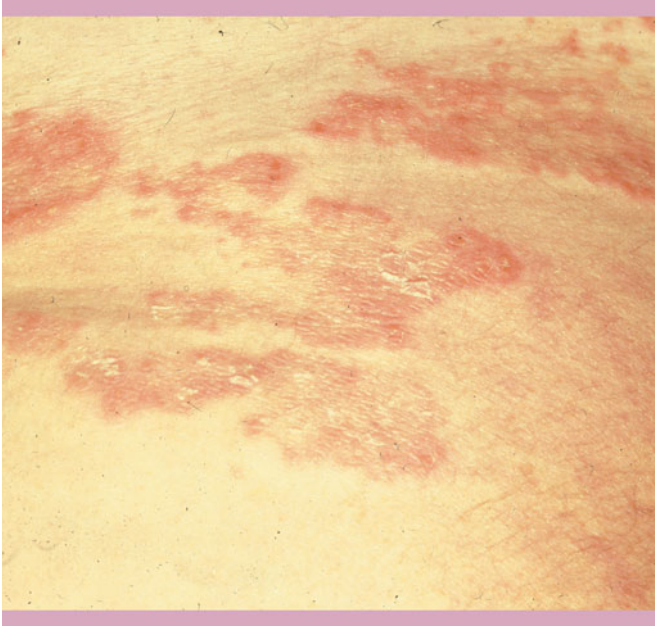


FIGURE 22-5 Subacute cutaneous lupus erythematosus. (Courtesy of Dr. Robert Jordon.)

enzyme inhibitors, griseofulvin, terbinafine, tumor necrosis factor antagonists

- Laboratory tests
 - Antinuclear antibody (ANA)
 - Anti-Ro (SS-A) in 70%, anti-La (SS-B) in 30%
 - May be associated with rheumatoid factor positivity, hypocomplementemia, and an elevated ESR
- Positive lupus band test: complement and/or immunoglobulin along dermal-epidermal junction
- Histology: similar to SLE
- Treatment
 - Sun-protection
 - Hydroxychloroquine, other antimalarials (chloroquine, quinacrine), thalidomide, azathioprine, acitretin, mycophenolate mofetil, dapsone, clofazimine

CHRONIC CUTANEOUS LUPUS ERYTHEMATOSUS (CCLE)/DISCOID LUPUS (DLE)

- Chronic, scarring and photosensitive disease
- Occurs in 15% to 30% of patients with SLE, 5% of patients with DLE progress to SLE
- Female to male of 3:1
- Clinical
 - Begin as erythematous papules or plaques
 - Progresses to plaques with follicular plugging, scale, central hypopigmentation, and peripheral hyperpigmentation
 - Localized: head and neck affected, usually with asymmetrical lesions on the face, ears, and scalp (Fig. 22-6)

- Widespread: symmetric involvement of the trunk and extremities, more often progress to SLE compared to localized disease
- Lesions resolve with permanent scarring, including scarring alopecia
- Less photosensitive than other forms
- May involve mucous membranes
- Laboratory
 - ANA: 20%
 - Anti-Ro (SS-A): 1% to 3%
- Histology: similar to ACLE/SCLE, but with more marked periappendageal involvement and follicular plugging
- Direct immunofluorescence (DIF): 90% of patients on lesional skin
- Treatment
 - Corticosteroids (topical or intralesional)
 - Antimalarials (single or combination): hydroxychloroquine, chloroquine
 - Thalidomide
 - Oral retinoids
 - Azathioprine
 - Mycophenolate mofetil
 - Methotrexate



FIGURE 22-6 Chronic cutaneous lupus erythematosus (CCLE). (Courtesy of University of Texas Medical School, Dermatology Resident Teaching Collection.)

CUTANEOUS LUPUS VARIANTS

- Tumid lupus erythematosus (TLE)
 - May be a variant of CCLE or SCLE
 - Low incidence of SLE
 - Non-scaling nodular lesion
 - Photosensitive
 - Histology shows mucin and interstitial lymphocytic infiltrate no epidermal involvement
 - Treatment: antimalarials
- Bullous systemic lupus erythematosus (BLE)
 - Subepidermal blistering disease that is seen in patients with SLE
 - *Three types:*
 - Antibodies to type VII collagen
 - Undetermined antigen location
 - Antigen in the epidermis
 - Clinical:
 - Patients must fulfill the criteria for SLE
 - Sudden onset of vesiculobullous lesions on an erythematous base, painful mucosal lesions
 - Most commonly affects upper trunk, proximal extremities, neck and face
 - Erosions result after rupture of the bullae which heal with hyper or hypopigmentation
 - Laboratory tests
 - Serologies: similar to SLE (see above)
 - Histology: subepidermal blister with neutrophils in the dermis
 - DIF: granular IgG, IgA, IgM and C3 at the dermal-epidermal junction
 - IIF: antibodies to collagen type VII
 - Treatment: dapsone
- Lupus erythematosus panniculitis/profundus (LEP) (Fig. 22-7):
 - Primarily affects deep dermis and subcutaneous fat
 - Occurs in SLE and CCLE patients, or as an isolated phenomenon
 - Clinical:
 - Chronic recurrent course
 - Tender, firm, subcutaneous nodules, often heal with prominent fat atrophy
 - Most commonly on proximal extremities, trunk, breasts, buttocks, and face (vs. erythema nodosum, which involves the calves)
 - Histolog: dermal perivascular and periappendageal lymphocytic inflammation that extends into the subcutaneous fat; lobular panniculitis with lymphocytes, lymphoid nodules with germinal centers, plasma cells, and histiocytes, hyalinized fat necrosis possible epidermal atrophy and hydropic degeneration of the basal cell layer
 - IF: IgM at the basement membrane
 - Treatment: similar to other forms of cutaneous LE
- Hypertrophic discoid lupus erythematosus:



FIGURE 22-7 Lupus panniculitis. (Courtesy of Dr. Robert Jordon.)

- Rare variant of DLE with markedly hyperkeratotic or verrucous lesions
- Often seen on the extensor extremities and face
- Mimics squamous cell carcinoma, clinically and histologically
- Chilblain lupus erythematosus (CHLE):
 - Red-purple papules and plaques on the fingers, toes, heels, elbows, knees, and nose precipitated by cold
 - Lesions develop scale and frequently scar
 - Usually occurs in patients with DLE
- Neonatal lupus erythematosus (NLE):
 - Caused by mother's antibodies (anti-Ro (95%), anti-La, or U1-ribonucleoprotein) in the fetus
 - Mothers are usually asymptomatic at the time of childbirth, but may have numerous autoimmune conditions (i.e., SLE, Sjogren's syndrome)
 - Maternal HLA-B8 and HLA-DR3
 - Affects 1% to 5% of infants with positive maternal anti-Ro antibodies
 - Mothers with an infant with NLE have a 25% incidence of having a subsequent affected child
 - Ro52 protein cardiac 5-HT₄ serotonergic receptor affected by maternal autoantibodies resulting in inhibition of serotonin activated L-type calcium currents (I_{Ca})
 - Clinical (Fig. 22-8)
 - Cutaneous SCLE-like lesions in 50% with well-demarcated, annular, erythematous, scaling plaques
 - ▲ Frequently periorbital ("owl-eye")
 - ▲ Photosensitive, with lesions on the scalp, neck, and face



FIGURE 22-8 Neonatal lupus erythematosus (NLE).
(Courtesy of Dr. Robert Jordon.)

- ▲ Present at birth in 66% of infants, 33% develop lesions within the first 2–5 months of life
- Congenital heart block (15% to 30%): complete heart block requires a pacemaker; patients may develop heart failure
- Hepatosplenomegaly may occur
- Hematologic changes: leukopenia, thrombocytopenia, anemia
- Laboratory tests
 - ANA
 - Maternal and neonatal anti-Ro, anti-La, anti-U1-RNP, anti-ds DNA
 - CBC, LFTs
 - Neonatal electrocardiography, echocardiography
 - Histology: hyperkeratosis, vacuolar degeneration of basal cell layer
 - IF: granular IgG at the dermal-epidermal junction
- Treatment
 - Photoprotection
 - Mild topical steroids
 - Congestive heart failure: early placement of a pacemaker

Antiphospholipid Syndrome (APS)

- Autoimmune disorder of unknown etiology, characterized by increased thrombosis and/or increased incidence of spontaneous abortions. Subgroups of APS patients—those with and those without the

presence of other risk factors for arterial or venous thrombosis

- Diagnosis of antiphospholipid syndrome requires the presence of one clinical criterion and one laboratory criterion
- Clinical criteria
 - Vascular thrombosis:
 - Arterial thrombosis
 - Venous thrombosis
 - Small vessel thrombosis of any organ/tissue confirmed by Doppler
 - Pregnancy morbidity:
 - Spontaneous abortion of a normal fetus at or after the 10th week of gestation
 - Premature birth of normal neonate at or before 34th week gestation due to severe preeclampsia, eclampsia, or placental insufficiency
 - Three or more unexplained consecutive miscarriages before ten weeks gestation
- Laboratory criteria (2 or more occasions 6 weeks or more apart)
 - IgG, IgM or anticardiolipin antibody (aCL) in medium or high titer
 - Anti-beta 2 glycoprotein
 - Lupus anticoagulant
- Other clinical findings (not included as part of criteria)
 - Cutaneous findings: superficial phlebitis, leg ulcers, distal ischemia, blue toe syndrome
 - Neurologic: transient ischemic attack, ischemic stroke, chorea, seizures, dementia, transverse myelitis, encephalopathy, migraines, pseudotumor cerebri, cerebral venous thrombosis, mononeuritis multiplex
 - Cardiac: myocardial infarction, valvular vegetations, intracardiac thrombi, atherosclerosis
 - Renal: renal vein/artery thrombosis, renal infarction, acute renal failure, proteinuria, hematuria, nephritic syndrome
 - Gastrointestinal: Budd-Chiari syndrome, hepatic/gallbladder/intestinal/splenic infarction, pancreatitis, ascites, esophageal perforation, ischemic colitis
 - Venous thrombosis: extremities/adrenal/hepatic/mesenteric/splenic vein/vena cava thrombosis
 - Endocrine: adrenal/testicular/pituitary infarction
 - Obstetric complications: spontaneous abortion, intrauterine growth retardation, hemolytic anemia, elevated liver enzymes, thrombocytopenia
 - Hematologic: thrombocytopenia, hemolytic anemia, hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura
 - Ophthalmic: retinal vein/artery thrombosis, amaurosis fugax (temporary loss of vision in one

- eye caused by decreased blood flow [ischemia] to the retina)
- SNAP syndrome: clinical manifestations of APS, without the presence of antibodies
- Conditions associated with the presence of aPL antibodies:
 - Autoimmune diseases: SLE, Sjogren's syndrome, rheumatoid arthritis
 - Infections: syphilis, hepatitis C, human immunodeficiency virus, malaria, leprosy, parvovirus B19, cytomegalovirus
 - Medications: procainamide, quinidine, propranolol, hydralazine, phenytoin, chlorpromazine, interferon alpha, quinine, amoxicillin, sulfadoxine/pyrimethamine (fansidar), and cocaine
- HLA associated with aPL antibodies: *DRw53*, *DR7*, *DR4*
- Catastrophic antiphospholipid syndrome (CAPS): acute onset, criteria include: evidence of involvement of ≥ 3 organ systems, and/or tissue development of manifestations simultaneously or in < 1 week, confirmation by histopathology of small-vessel occlusion in at least one organ/tissue laboratory confirmation of the presence of aPL (lupus anticoagulant and/or aCL an/or anti-B-2-GP I)
- Laboratory studies: (presence of antibodies on 2 or more occasions at least 12 weeks apart)
 - Antiphospholipid (aPL) antibodies
 - Anticardiolipin (aCL) antibodies
 - Anti- β_2 -glycoprotein I antibodies
 - Other antibodies to phosphatidylserine, phosphatidylthreonine (membrane phospholipids)
 - Activated partial thromboplastin time (aPTT)
 - Lupus anticoagulant (LA) test such as dilute Russell viper venom time (DRVVT)
 - False-positive serologic test result for syphilis
 - Complete blood cell count (thrombocytopenia, Coombs-positive hemolytic anemia)
 - Proteinuria and renal insufficiency from thrombotic microangiopathy
 - 45% of patients have a positive ANA
 - Ultrasound (evaluate for DVT); CT or MRI of chest (evaluate for pulmonary embolism), brain (evaluate for cerebral vascular accident), abdomen (evaluate for Budd-Chiari syndrome)
- Treatment
 - Following thrombosis: anticoagulation with intravenous heparin, followed by warfarin, heparin or low-molecular-weight (LMW) heparin
 - Recurrent spontaneous abortions: treated with subcutaneous heparin 7,500 to 12,000 units twice daily along with aspirin 81 mg daily
 - Thrombocytopenia: prednisone

Sjögren's Syndrome (SS)

- Autoimmune disease that mainly affects the exocrine glands
- HLA-DR3 and HLA-DR52 in patients with primary SS
- Primary SS has xerophthalmia and xerostomia only
- Secondary SS has xerophthalmia and xerostomia and occurs with rheumatoid arthritis, SLE, SSc, DM, and MCTD
- SS criteria
 - Presence of four out of six criteria, as long as either the histopathology or serology is positive:
 - Ocular symptoms of dryness
 - Oral symptoms of dryness
 - Ocular signs—a positive result for at least one of the following two tests:
 - ▲ Schirmer's test
 - ▲ Rose Bengal score or other ocular dye score
 - Histopathology: focal lymphocytic sialoadenitis, with a focus score of 1 per 4 mm² of glandular tissue
 - Salivary gland involvement—a positive result for at least one of the following diagnostic tests:
 - ▲ Unstimulated whole salivary flow (< 1.5 mL in 15 min)
 - ▲ Parotid sialography showing the presence of diffuse sialectasias, without evidence of obstruction in the major ducts
 - ▲ Salivary scintigraphy showing delayed uptake, reduced concentration, and/or delayed excretion of tracer
 - Autoantibodies: presence in the serum of the following autoantibodies: Ro(SSA) or La(SSB) antigens, or both
- Clinical findings
 - Keratoconjunctivitis sicca: xerophthalmia
 - Bilateral parotid swelling (most common sign in children)
 - Unstimulated salivary flow less than 1.5 mL/min
 - Positive Schirmer's test showing decreased tear film for eyes
 - Xerostomia (Fig. 22-9): signs of reduced salivary flow, associated with angular cheilitis, dental caries, oral candidiasis with resulting erythema and atrophy of the dorsum of the tongue or a white, cheesy curd that bleeds when wiped off
 - Extraglandular symptoms
 - Hepatitis (13%): also increased incidence of primary biliary cirrhosis
 - Arthritis (42%)
- Laboratory studies
 - Anti-Ro/SS-A (90%) \pm anti-La/SS-B (70%)
 - Rheumatoid factor
 - Antithyroglobulin antibodies (25%)



FIGURE 22-9 Sjögren syndrome (SS). (Courtesy of Dr. Bela B. Toth.)

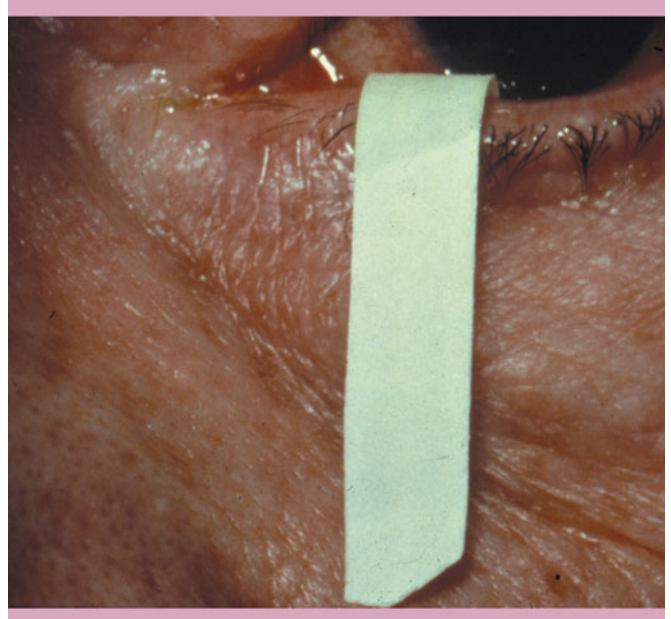


FIGURE 22-10 Positive Schirmer test. (Courtesy of Dr. Robert Jordon.)

- B-lymphocyte infiltration (20% to 25%) and CD4 + T-cell infiltration (70% to 80%) localized in the salivary glands
- Positive Schirmer's test (Fig. 22-10): measures lacrimation response in the eye; filter paper strip placed in lower conjunctival sac and the wetting length achieved in 5 minutes is measured; greater than 8 mm in 5 minutes is abnormal
- Histopathology: minor salivary gland: mononuclear inflammatory infiltrates, interstitial fibrosis, and acinar atrophy
- Treatment: symptom control; no curative agent exists
 - Topical cyclosporine A (Restasis): 0.05% to 0.1% ophthalmic drops
 - Pilocarpine HCl (Salagen): 5 mg tablets, cholinergic agonist
 - Cevimeline HCl (Evozac): 30 mg tablets, cholinergic agonist binding to muscarinic receptors
 - Plaquenil (hydroxychloroquine)

MIXED CONNECTIVE TISSUE DISEASE (MCTD)

- Disease syndrome with overlapping features of systemic sclerosis, systemic lupus erythematosus (SLE) and polymyositis
- Associated with HLA-DR4 or HLA-DQB1
- Controversy exists as to whether MCTD constitutes a distinct clinical entity
- Alarcon-Segovia and Villareal classification
 - Serologic criterion is a positive anti-RNP at a titer of 1:1600 or higher
 - Clinical criteria; presence of at least 3 of the following:
 - Edema of the hands
 - Raynaud's phenomenon
 - Acrosclerosis
 - Synovitis
 - Myositis (laboratory or biopsy diagnosis)
- Kusunokawa diagnostic criteria for mixed connective tissue disease (MCTD)
- Requirement for diagnosis: at least one *common symptom*, with positive U1 RNP antibodies and one or more findings in at least two of the three categories A, B, and C from the *mixed findings* list
- *Common symptoms*
 - Raynaud's Phenomenon
 - Swollen fingers or hands
 - Presence of Anti U1 RNP
- *Mixed findings*
 - Systemic lupus erythematosus (SLE)-like
 - Polyarthrititis
 - Pericarditis/pleuritis
 - Lymphadenopathy
 - Facial erythema
 - Leukopenia/thrombocytopenia
 - Scleroderma-like
 - Sclerodactyly
 - Pulmonary fibrosis
 - Esophageal dysmotility

- Polymyositis-like
 - Muscle weakness
 - High creatine phosphokinase (CPK)
 - Myopathic electromyogram (EMG)
- Other clinical features
 - Arthralgias in 60%
 - Sclerodactyly
 - Interstitial lung disease, pulmonary hypertension (most common cause of death)
 - Abnormal nailfold capillaries (50%)
 - Palpable purpura (25%)
 - Vascular disturbances may lead to peripheral gangrene/leg ulcers
 - Dysphagia and dysfunction of esophageal motility
- Laboratory studies
 - CBC
 - Muscle enzymes: creatine kinase, aldolase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactic dehydrogenase
 - Anti-RNP, anti-Smith, anti-Ro(SSA), anti-La(SSB), anti-Scl-70, phospholipids, anti-cardiolipin and histone, complement: C3, C4,
 - High-titer ANA in a speckled pattern
 - Antibodies against U1—70-kDa small nuclear ribonucleoprotein (snRNP) at titer > 1:1600
 - Histology: myositis
 - Other tests: chest x-ray, barium swallow (evaluate esophageal motility)
 - Echocardiography: (evaluate myocardial function and pulmonary artery pressure)
- Treatment
 - Corticosteroids, hydroxychloroquine, Cyclophosphamide, azathioprine, methotrexate
- Classic DM with associated connective tissue disease
- Clinically amyopathic DM (CADM)
 - ▲ Amyopathic DM (ADM)/dermatomyositis sine myositis: no clinical or lab evidence of myositis for 6 months without treatment
 - ▲ Hypomyopathic DM (HDM): no clinical evidence of myositis, but lab evidence of subclinical disease
- Polymyositis (PM), similar clinical feature to DM: inflammatory myopathy with symmetric muscle weakness
- Juvenile DM (JDM)
 - Classic JDM
 - Clinically amyopathic JDM
- Clinical
 - Cutaneous findings:
 - Occur 2 to 3 months prior to muscle weakness
 - Primary lesion: pruritic erythematous-violaceous patches and plaques with or without scale. Poikiloderma may be present. Lesions frequently involve scalp, anterior/posterior neck, photoexposed areas and extremities, but can involve any body area
 - *Heliotrope rash*: first cutaneous sign: periorbital, symmetric, violaceous patches with or without edema
 - *Gottron's papules*: violaceous papules overlying the following joints of the dorsal hands: metacarpophalangeal, distal interphalangeal, and/or proximal interphalangeal
 - *Gottron's sign*: violaceous symmetric macular erythema over bony prominences of hands and elsewhere (e.g., elbows, knees, medial malleoli)
 - *Tendon streaking*: linear violaceous erythema along extensor tendons of hands/feet
 - *Nailfold capillary changes*: correlated with disease severity; capillary telangiectasia, infarcts, capillary loop dropout (whitish areas of avascularity—not seen in LE), Samitz sign cuticular dystrophy
 - *V-sign*: macular erythema and poikiloderma of V-area of neck and chest
 - *Shawl sign*: macular erythema and poikiloderma of upper back and shoulders
 - *Holster sign*: erythematous patches/plaques on bilateral hips
 - *Malar rash*: erythema of the central face but unlike ACLE, usually does not spare nasolabial folds
 - *Mechanics hands*: hyperkeratosis of the palmar and lateral surfaces of the fingers, associated with interstitial lung disease
 - *Calcinosis cutis*: cutaneous calcium deposition, usually in areas of trauma, associated with

Dermatomyositis (DM)

- Idiopathic inflammatory myopathy with characteristic cutaneous lesions with or without muscle inflammation and weakness
- Diagnostic criteria: (3 criteria plus the rash)
 - Symmetrical muscle weakness: limb girdle muscles and anterior neck flexors
 - Muscle biopsy: evidence of muscle fiber necrosis, inflammatory exudate, often perivascular
 - Elevated muscle enzymes: CPK, aldolase, LDH
 - EMG triad: small polyphasic action potentials, positive sharp waves and insertional irritability and bizarre high frequency repetitive discharges
 - Cutaneous changes: heliotrope rash with periorbital edema; scaly dermatitis
- Classification
 - Adult dermatomyositis:
 - Classic DM
 - Classic DM with malignancy

- increased disease activity, 10% of adult DM patients
- Extracutaneous findings
 - Proximal symmetric muscle weakness (shoulder and limb girdle)
 - Dysphagia/dysphonia (esophageal/pharyngeal involvement)
 - Pulmonary disease:
 - ▲ Restrictive lung disease from respiratory muscle weakness
 - ▲ Interstitial lung disease: in 25% to 65% of patients, can be rapidly progressive and fatal, a leading cause of mortality
 - Synovitis
 - Raynaud's phenomenon
 - Cardiac disease: rare ECG changes, arrhythmias, cardiomyopathy
- Juvenile DM (JDM):
 - Similar cutaneous features of classic DM in patients younger than 18 years
 - Other clinical features
 - *Vasculopathic lesions* (SQ nodules, digital ulcers) poorer prognosis
 - *Calcinosis cutis*: occurs on bony prominences; 40% of children
 - *Acquired lipodystrophy* (prevalence of 10% to 40%), generalized, partial, or focal, late complication of JDM, associated with more severe, chronic disease and with other disease sequelae such as calcinosis, insulin resistance, diabetes, and hypertriglyceridemia
 - *Cardiac*: Asymptomatic cardiac conduction delays or right bundle branch block (up to 50% of patients)
 - Thrombospondin-1, a mediator of angiogenesis, is increased in patients with juvenile DM
- DM associated with malignancy
 - Reported rate of malignancy in adults varies widely: 13% to 25%; there is no reported increased risk in JDM patients
 - May precede, coincide with, or follow the diagnosis of DM
 - Risk remains elevated for 3–5 years following diagnosis
 - Presence of malignancy represents a major indicator of poor prognosis in DM
 - Association between a rapid onset of the disease and malignancy
 - Relative risk for ovarian cancer in female patients is 16.7
 - Reported association with the following malignancies: breast (adenocarcinoma most common), gastrointestinal, ovarian, lung
- Drug-induced dermatomyositis: statins, hydroxyurea, penicillamine
- Poor Prognosis associated with: progressive disease, dysphagia, extensive cutaneous lesions on the trunk, cardiac issues, longer duration of symptoms before diagnosis, initiation of therapy after 24 months of muscle weakness, older age, malignancy, progressive disease
- Diagnosis
- *Myositis-specific antibodies* (not seen in other CTD patients):
 - Mi-2: nuclear helicase, 5% of PM/DM, 15% to 20% of DM
 - Associated with classic DM, V/shaw sign, cuticular dystrophy
 - Good prognosis
 - *Antisynthetase antibodies*
 - Antibodies to aminoacyl-tRNA synthetases, cytoplasmic antigens
 - *Anti-EJ*: associated with typical skin lesions
 - *Anti PL-12 and PL-7*: prevalence of 25% for both
 - Jo-1 (15% to 20% DM/PM)
 - Associated with antisynthetase syndrome:
 - ▲ Mechanic's hands
 - ▲ Myositis (may or may not have cutaneous DM)
 - ▲ Interstitial lung disease
 - ▲ Synovitis
 - ▲ Raynaud's phenomenon
 - ▲ Patients often refractory to treatment
 - *Annexin XI* (56-kDa): most sensitive for juvenile DM
 - *Anti-CADM-140*: found in 50% of CADM patients
 - *Anti-p155kD*: malignancy-associated DM
 - Anti-antisignal recognition protein (SRP): associated with severe polymyositis
 - *Other antibodies* (myositis-associated, not DM-specific):
 - ANA: positive in 60% to 80%, more commonly positive in CADM
 - SS-A/Ro
 - *Anti-PM-Scl* (seen in overlap of DM/PM and scleroderma)
 - *AntiKu* (seen in overlap of DM and with scleroderma and/or SLE)
- Laboratory studies
 - Elevation of the following: creatine kinase level (most sensitive for myositis), aldolase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH)
 - Elevated erythrocyte sedimentation rate
 - Muscle studies: electromyogram (EMG) shows a myopathic pattern, muscle biopsy, MRI
 - Histology: epithelial vacuolar changes with lymphocytic infiltrate at the dermal epidermal junction, identical to findings of CLE

- DIF: C5b-9 deposition at DEJ and perivascularly
- Malignancy workup in all patients with localizing symptoms and patients > 40 years of age at presentation and annually
- Endoscopic studies of the upper and lower gastrointestinal tract should be done according to the patient's age
- Treatment
 - Systemic corticosteroids for muscle involvement
 - Steroid-sparing agents for maintenance: methotrexate, azathioprine, cyclosporine, mycophenolate mofetil; antimalarials as adjuncts for mild skin disease
 - IV immunoglobulin (IVIG): useful for severe and refractory disease, pulmonary disease
 - Cyclophosphamide: for interstitial lung disease
 - Biologics: rituximab, tumor necrosis factor inhibitors (entercept, infliximab)
 - Topical tacrolimus: for skin disease

Systemic Sclerosis (SSc)

- Multisystemic connective tissue disease with excessive collagen deposition and vasomotor disturbances
- Associated with HLA-B8, HLA-DR5, HLA-DR3, HLA-DR52, and HLA-DQB2
- Pathophysiology also associated with: genetic, environmental, vascular, and autoimmune factors
- Five forms of systemic sclerosis: diffuse systemic sclerosis (dSSc), limited systemic sclerosis (lSSc), transitory form (dSSc/lSSc), systemic scleroderma sine scleroderma, and malignant scleroderma
- Other factors associated with SSC pathophysiology:
 - Environment-related
 - *Criteria for diagnosis of adult SSc:* diagnosis when 1 major and 2 minor criterion are present
 - Major features include centrally located skin sclerosis that affects the arms, face, and/or neck
 - Minor features include sclerodactyly, erosions, atrophy of the fingertips, and bilateral lung fibrosis
- Clinical findings
 - Mucocutaneous findings
 - *Cutaneous sclerosis:* progresses through 3 phases
 - Edematous phase: fingers with edema (“puffy phase”)
 - Indurated or sclerotic phase: thickened tight skin, hair loss and decreased sweating, begins acraly and on face/neck, proximal spread, sclerodactyly: fingertip tapering, loss of finger-pad pulp, pitted scars, digital ulcers (35%) and loss of mobility (Fig. 22-11)
 - Atrophic, or late phase: dermis is firmly adherent to underlying subcutaneous fat



FIGURE 22-11 Sclerodactyly. (Courtesy of Dr. Melissa Costner.)

- *Salt-and-pepper dyspigmentation:* vitiligo-like depigmentation with perifollicular pigment
- *Skin ulceration:* digital tip ulcers (secondary to ischemia); ulcers over the bony prominences (attributable to contractures)
- *Calcium deposits:* subcutaneous and/or intracutaneous calcinosis (Fig. 22-12)
- *Nailfold capillary changes:* capillary loop dilatation alternating with loop dropout; occurs in 90% of patients
- *Ocular symptoms:* dry eyes, blepharitis, retinal hemorrhages (with renal crisis)
- *Oral symptoms:* xerostoma, dental decay

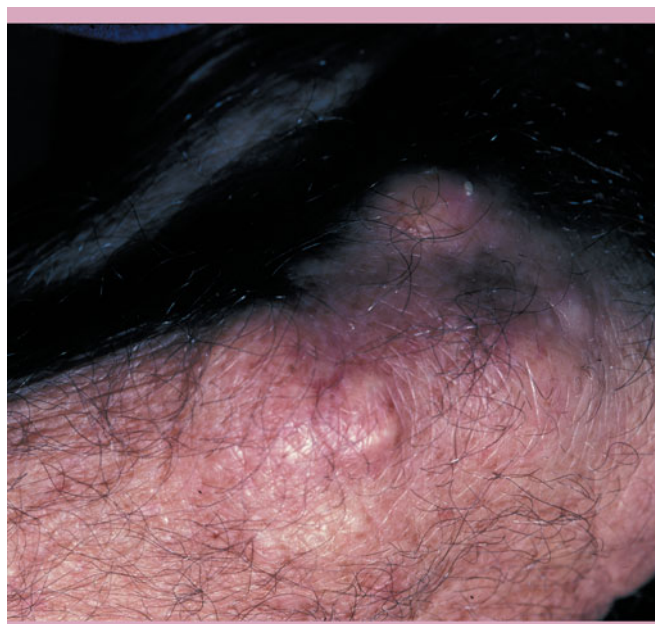


FIGURE 22-12 Calcinosis cutis. (Courtesy of Dr. Robert Jordon.)

- *Raynaud's phenomenon*
 - Paroxysmal vasospasm of digits in response to cold exposure or emotional stress
 - Endothelial injury results in intimal hyperplasia and fibrosis
 - 95% of SSc patients
 - 3 pathogenic mechanisms—vasoconstriction, ischemia, and reperfusion (white-blue-red appearance of the skin)
 - Typically the first clinical and most common sign of SSc, may precede the disease by 5–10 years
 - Types of Raynaud's: primary: acral color changes are the only clinical signs without any other symptom and disease; secondary: color changes are associated with clinical symptoms or signs of systemic disease
- Musculoskeletal
 - *Muscle weakness*: scleroderma myopathy (proximal muscle weakness) and sclerodermatomyositis (true overlap between scleroderma and polymyositis with severe muscle weakness and elevated CPK and abnormal EMG)
 - *Arthritis*; symmetric polyarthralgia and joint stiffness (with or without gross synovitis),
 - *Tendon fibrosis*: may result in myalgia, joint pain, immobility, contractures and fibrinous tenosynovitis with friction rub
- Gastrointestinal tract (affects 75% to 90% of patients)
 - *Esophageal dysmotility*
 - ▲ 90% of patients, occurs in early disease, secondary to smooth muscle fibrosis
 - ▲ may lead to gastroesophageal reflux disease with symptoms of heartburn, dysphagia and resulting in complications of Barrett's esophagus and esophagitis (may cause esophageal stricture)
 - *Gastric vascular ectasia* may lead to gastroparesis
 - *Small intestinal muscle fibrosis* may lead to functional ileus (pseudoobstruction); bacterial overgrowth may cause malabsorption and diarrhea
 - *Colonic signs and symptoms*: megacolon, constipation and diverticula
- Pulmonary disease: 70% of SSc patients; main cause of mortality
 - *Pulmonary interstitial fibrosis*: occurs in early disease, most commonly with diffuse SSc
 - *Pulmonary artery hypertension (PAH)*: 10% to 15% of patients, occurs later in the course of the disease, three types: severe isolated PAH without significant fibrosis (common in lSSc), PAH with fibrosis (common in dSSc), and lastly an indolent PAH
- Renal
 - *Scleroderma renal crisis (SRC)*, usually in dSSc (18% of patients): hypertension and oliguric renal failure
- Cardiac
 - Myocardial fibrosis (<5% of dSSc), congestive heart failure, myocarditis, pericarditis, ventricular arrhythmias
- Genitourinary
 - Erectile dysfunction (12% to 60%)
 - Dyspareunia
- Clinical features of the two most common forms
 - Diffuse cutaneous sclerosis (dSSc):
 - Associated with topoisomerase I (Scl-70) in 30%
 - Quick progression of sclerosis of proximal limbs and trunk
 - Associated with pulmonary interstitial fibrosis in 30% to 60%, scleroderma renal crisis
 - Limited systemic sclerosis (lSSc):
 - Also known as CREST (calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly, telangiectasia)
 - Anticentromere antibodies in 40% to 50%
 - Sclerosis confined to face, neck, and extremities distal to elbows/knees
 - Slowly progressive and indolent
 - Late phase:
 - ▲ Calcinosis cutis: calcium apatite crystals found in tissue
 - ▲ Matte-like telangiectasias: can also occur with dSSc
 - ▲ Pulmonary artery hypertension: leading cause of death in lSSc
- Juvenile systemic sclerosis:
 - Children under 16 years of age account for less than 5% of all cases of SSc
 - Fourfold more frequent in girls
 - Raynaud's phenomenon (RP) is the first sign of the disease in 70% of patients
 - Classification criteria for JSSc: (replaces previous adult classification criteria)
 - Sensitivity of 90%, a specificity of 96%
 - Patient, less than 16 years, with one major and at least two of the 20 minor criteria
- *Major criterion*: proximal sclerosis/induration of skin
- *Minor criteria*
 - Skin: sclerodactyly
- Vascular: Raynaud's phenomenon, nailfold capillary abnormalities, digital tip ulcers
- Gastrointestinal: dysphagia, gastro-esophageal reflux
- Renal: renal crisis, new-onset arterial hypertension
- Cardiac: arrhythmias, heart failure
- Respiratory: pulmonary fibrosis (high resolution computed tomography/radiograph), diffusing

- lung capacity for carbon monoxide, pulmonary hypertension
- Musculoskeletal: tendon friction rubs, arthritis, myositis
 - Neurologic: neuropathy, carpal tunnel syndrome
 - Serology: antinuclear antibodies, SSc-selective autoantibodies (anticentromere, antitopoisomerase I, antifibrillarin, anti-PM-Scl, anti-fibrillin or anti-RNA polymerase I or III)
 - Scleroderma-like disorders:
 - Localized scleroderma, disorders with mucin deposition: scleromyxedema, Buschke scleredema, nephrogenic fibrosing dermopathy, disorders with monoclonal gammopathy: scleromyxedema, POEMS syndrome, myeloma with scleroderma-like changes, disorders with eosinophilia: diffuse fasciitis with eosinophilia, eosinophilia-myalgia syndrome, toxic oil syndrome
 - Disorders with defined metabolic/biochemical/endocrine abnormalities: insulin dependent diabetes mellitus (IDDM), non-insulin dependent diabetes mellitus (NIDDM), carcinoid syndrome, porphyria, phenylketonuria, nephrogenic fibrosing dermopathy, chronic graft-versus-host disease
 - Chemically induced scleroderma-like disorders: eosinophilia-myalgia syndrome, toxic oil syndrome, polyvinyl-chloride disease, organic solvents, epoxy resins exposure
 - Drug induced scleroderma-like disorders: bleomycin, injections of pentazocine, progestin, vitamin B₁₂, vitamin K, cocaine, d-penicillamine, peplomycin, interferon-β1a, uracil-tegafur, paclitaxel, methysergide, gemcitabine, physical injury (trauma, vibration stress, radiation)
 - Inherited progeroid syndromes (Werner's syndrome), heterogeneous group of hereditary disorders with skin thickening (melorheostosis, stiff skin syndrome, porphyria cutanea tarda, phenylketonuria), or tight skin (restrictive dermopathy, scleroderma-like Huriez syndrome)
 - Laboratory studies
 - Autoantibodies:
 - ANA: 15% to 40% of patients; 81% to 97% in JSSc, most commonly speckled, nuclear, centromere
 - *Topoisomerase I*: (by immunodiffusion), 9% to 20% of adult patients, 20% to 34% in JSSc; associated with diffuse cutaneous involvement, increased mortality rate, due to ventricular failure secondary to pulmonary disease (interstitial fibrosis)
 - *Centromere*: 20% to 30% of patients, most commonly found with ISSc; associated with a higher risk for calcinosis and ischemic digital loss, lower frequency of interstitial pulmonary fibrosis, increased risk of pulmonary hypertension
 - *Fibrillarin (U3-RNP)*: less than 10% of patients with SSc, associated with diffuse cutaneous disease
 - *RNA Polymerases (I-III)*: specific for SSc, 20% of patients, associated with diffuse cutaneous involvement and SSc-related renal crisis, greater mortality
 - *PM-Scl* (2% of patients with scleroderma): found in patients with myositis, scleroderma, and the polymyositis-scleroderma overlap syndrome, (myositis, Raynaud phenomenon, arthritis, and interstitial lung disease)
 - *Anti-Th/To*: 2% to 5% of patients with SSc and are associated with milder skin and systemic involvement, except for more severe pulmonary fibrosis
 - *Anti-ku antibodies*: scleroderma-myositis overlap syndromes and a wide spectrum of rheumatic diseases
 - *Antiphospholipid antibodies (aPL)*: 20% to 25% of patients, increased frequency of pregnancy losses; anticardiolipin antibodies (aCL): thrombosis and pulmonary hypertension
 - *Anti-U1RNP*: 8% of patients, less cutaneous and renal involvement and favorable response to corticosteroids
 - *Anti-Ro antibodies*: < 35% of patients, association of SSc with Sjögren syndrome up to 20%
 - Imaging studies
 - Chest radiograph: fibrosis of the lower areas of the lungs
 - Bone radiography: generalized osteopenia
 - Doppler echocardiography: left- and right-sided heart diseases
 - Pulmonary function test
 - Cine esophogram: evaluate for esophageal hypomotility
 - Esophagogastroduodenoscopy: identify erosive esophagitis, superinfection, Barrett's esophagus, ulceration, and malignant transformation
 - Small bowel series: identifies characteristic hypomotility
 - Histologic findings
 - Appendageal atrophy; marked mucopolysaccharide, glycoprotein, and compact collagen (types I and III) deposition in the dermis; subintimal proliferation of small arteries and arterioles
 - Treatment
 - Pulmonary: vaccinations (prophylactic influenza and *Streptococcus pneumoniae*), cyclophosphamide for alveolitis; prostacyclin (epoprostenol and treprostinil), endothelin-1 antagonist (bosentan), and phosphodiesterase type-5 inhibitor (sildenafil) for PAH

- Cardiac: nonsteroidal anti-inflammatory drugs or low-dose corticosteroids for pericarditis, high dose corticosteroids for myocarditis. Digitalis and diuretics are also used
- Renal: ACE inhibitors, dialysis, renal transplant
- Raynaud's, digital ulcers: calcium-channel blockers (nifedipine), topical nitropaste, phosphodiesterase type 5 inhibitor (sildenafil), ACE inhibitors
- Musculoskeletal: NSAIDs
- Skin disease: UVA1 phototherapy, antifibrotic agents (e.g., D-penicillamine, interferon- α and interferon- γ)
- Scleroderma renal crisis: IV captopril
- Gastrointestinal tract involvement: proton pump inhibitors (e.g., omeprazole), H₂ blockers, cisapride, and metoclopramide, endoscopic dilatation, sclerotherapy for ectatic vessels, broad spectrum antibiotics for bacterial overgrowth
- Other systemic treatments: cyclophosphamide, methotrexate, chlorambucil, 5-fluorouracil, stem cell transplantation

Localized Scleroderma (Morphea)

- Idiopathic fibrosis of the skin and adjacent structures
- Prognosis is good. Progression to systemic sclerosis is rare; lesions tend to regress spontaneously over 3 to 5 years, usually with residual pigmentary and atrophic changes
- Subtypes: plaque, generalized, bullous, linear, and deep
- Etiology
 - Role of autoimmunity in the pathogenesis of morphea
 - Autoimmune conditions associated with morphea: Hashimoto's thyroiditis, vitiligo, systemic lupus erythematosus, and type 1 diabetes mellitus
 - Cytokines and growth factors released by endothelial and inflammatory cells (TH2 activation) result in fibroblast proliferation and increased deposition of extracellular matrix
 - Factors involved in promoting fibrosis in morphea: transforming growth factor- β (TGF- β), connective tissue growth factor (CTGF), IL-1, IL-4, IL-6, endothelin-1, and tissue inhibitor of metalloproteinase-1.2 T
- Clinical findings
 - Excessive collagen deposition with thickening and induration of the skin and subcutaneous tissue
 - May begin with signs of inflammation, such as erythema and warmth
 - Usually asymptomatic, but may complain of pain or pruritus
 - Surface becomes smooth and shiny, lilac-colored

- Usually progresses over 3–5 years, then regresses, with skin softening and some residual atrophy/hyperpigmentation
- Types of morphea
 - *Plaque-type*:
 - Most common, occurs in more than 50% of cases of morphea
 - Indurated plaques 1 to 30 cm in diameter, may have an associated violaceous border (Fig. 22-13)
 - Lesions progressively become indurated, with a porcelain white or yellow hue and then heal with atrophy, depigmentation, or hyperpigmentation
 - Trunk involved more commonly than extremities
 - Variants: guttate, generalized, keloidal (nodular), atrophoderma of Pasini and Pierini



FIGURE 22-13 Plaque morphea. (Courtesy of University of Texas Medical School, Dermatology Resident Teaching Collection.)

- *Generalized morphea*: 13% of patients with morphea; coalescence of individual plaques or the development of multiple lesions in more than 2 anatomical sites; diffuse morphea: progression to involve widespread areas of the body
- *Nodular or keloid morphea*: sclerotic papules and plaques that resemble keloid scars
- *Guttate morphea*: multiple small, usually superficial papules
- *Atrophoderma of Pasini and Pierini*: possibly an end-stage form of plaque-type morphea; dermal/fat atrophy of trunk or proximal extremities with depressed plaques with a blue-brown, gray, or violaceous hue with a sharp cut-off and deep indentation
- *Deep morphea (morphea profunda)*: involves deep dermis, subcutaneous tissue, fascia, muscle, and bone, may calcify
- Variants:
 - *Subcutaneous morphea*: mainly subcutaneous involvement with rapid onset of symmetric sclerotic bound-down lesions and ill-defined borders
 - *Morphea profunda*: all skin layers with diffuse, taut, bound-down sclerosis
 - *Eosinophilic fasciitis* (or Shulman syndrome): see below
 - *Disabling pansclerotic morphea of children*: poor prognosis, diffuse full-thickness sclerosis of the trunk, face, and extremities, sparing the fingertips and toes, affects the deep subcutaneous tissue, fascia, muscle, and bone
 - *Bullous morphea*: tense subepidermal bullae may occur in plaques of morphea on the extremities, trunk, face, or neck and may be superficial or extend into the dermis
 - *Linear morphea*:
 - Accounts for approximately 20% of all cases; comprises up to 65% of cases of juvenile morphea
 - Linear plaques that become confluent and extend longitudinally, can impair mobility of an entire limb, can involve muscle/fascia/tendons, can impair joint mobility
 - ▲ *En coup de sabre*: affects frontoparietal scalp; rarely, may extend deeply; ocular complications such as eyelid lesions, exophthalmos, uveitis, episcleritis, xerophthalmia, papilledema, and glaucoma (up to 15% of cases); neurologic involvement with resulting seizures peripheral neuropathy, encephalitis, central nervous system vasculitis, vascular malformations, and/or strokes
 - ▲ *Progressive facial hemiatrophy* (Parry-Romberg syndrome): variant of linear morphea with progressive hemifacial atrophy; primary lesion occurs in the subcutaneous tissue, muscle, and bone (Fig. 22-14)
- Laboratory studies:
 - ANA:
 - Positive in 40% of plaque-type or generalized morphea
 - Positive in 67% of linear morphea
 - *Anti-single-stranded DNA*: 50% of morphea patients, especially correlates with linear morphea
 - *Antihistone antibodies (AHAs)*: 35% morphea patients
 - *Antifibrillar antibodies*: 30% morphea patients
 - *Rheumatoid factor (RF)*: 60% of patients
 - *Polyclonal hypergammaglobulinemia*: 50% of patients
 - *Antitopoisomerase II*: 76% in morphea patients
 - *Complete blood count*: in patients with eosinophilic fasciitis
 - *Neurologic and ophthalmologic examinations*: patients with morphea involving the face
 - Histology: *early lesions*: dense inflammatory infiltrate composed of lymphocytes, macrophages, plasma cells, *late lesions*: thickened, hyalinized collagen bundles
- Treatment
 - Topical or intralesional corticosteroids
 - Calcipotriene (vitamin D analog)
 - UVA-1 phototherapy
 - Imiquimod 5% cream



FIGURE 22-14 Parry romberg. (Courtesy of University of Texas Medical School, Dermatology Resident Teaching Collection.)

- Generalized, linear, and deep morphea: systemic corticosteroids, antimalarial agents, methotrexate, phenytoin, colchicine, and cyclosporine
- Physical therapy for linear morphea

Eosinophilic Fasciitis (EF, Shulman Syndrome)

- Disorder characterized by peripheral eosinophilia and fasciitis
- Scleroderma-like induration of the skin, differs from PSS since it usually spares the fingers, hands, and face and does not present with Raynaud's
- Belongs to the subtype of deep localized scleroderma or deep morphea
- Cause is unknown; however it has been reported in association with vigorous exercise, drugs, borreliosis, arthropod bites, and trauma
- Increased expression of genes for transforming growth factor β (TGF- β) and extracellular matrix proteins in fibroblasts
- Clinical findings:
 - Sudden onset of tender, edematous, and erythematous extremities associated with weakness and muscle pain with limited motility
 - Fascial involvement can lead to contractures (75%) and separation of muscle groups by a line of demarcation (groove sign)
 - Veins may appear depressed (sunken veins)
 - Rippling of the skin and a peau d'orange change often develops
 - Associated with severe cramps, distal sensorimotor neuropathy, mononeuritis multiplex, cognitive symptoms
 - Cardiopulmonary features: pneumonitis, respiratory muscle dysfunction, pulmonary hypertension
- Differential diagnosis
- Eosinophilia-myalgia syndrome: when EF is accompanied by muscle weakness; however, in eosinophilia-myalgia syndrome there are muscle pains, polyneuropathy or pulmonary disease, and a history of L-tryptophan intake (some cases of EF are reported after L-tryptophan ingestion, suggesting an overlap in the pathogenesis)
- Scleroderma, systemic sclerosis, and mixed connective tissue disorder: typical findings of these diseases include sclerodactyly, Raynaud's phenomenon, and the presence of antinuclear antibodies not found in EF
- Laboratory signs
 - Peripheral blood eosinophilia (64% of patients)
 - Hypergammaglobulinemia (75% of patients)
 - Erythrocyte sedimentation rate (50% to 70%)
- Histologic findings: inflammation, edema, thickening, and sclerosis of the fascia; presence of lymphocytes, plasma cells, histiocytes, and eosinophils, similar to scleroderma

- Imaging studies: ultrasound and magnetic resonance imaging in order to detect thickened fascia
- Treatment
 - Prednisone, hydroxyzine, ibuprofen, cimetidine, hydroxychloroquine, photochemotherapy and cyclophosphamide
 - Spontaneous remission can occur

Cryoglobulinemia

- Cryoglobulins: plasma immunoglobulins or immunoglobulin-containing complexes that precipitate on exposure to cold and redissolve on warming
- Types of cryoglobulins
 - *Type I*: (10% to 15%) monoclonal immunoglobulin, usually IgM or IgG
 - Associated with plasma cell dyscrasias/lymphoproliferative disorders
 - Clinically indistinguishable from those with Waldenström's macroglobulinemia, multiple myeloma, immunocytoma or chronic lymphocytic leukemia
- Clinical findings
 - ▲ Associated with signs of peripheral vessel occlusion
 - ▲ Patients may present with clinical manifestations related to hyperviscosity syndrome, purpura lesions, livedo reticularis acrocyanosis, Raynaud phenomena, ulcers and gangrene
- Mixed cryoglobulinemia (MC)
 - Etiological role of HCV in most cases of type II and III cryoglobulinemia
 - *Type II*: (50% to 60%) monoclonal IgM (rarely IgA or IgG that has rheumatoid factor (RF) activity and bind to polyclonal immunoglobulins (usually IgGs)
 - *Type III*: (25% to 30%) polyclonal IgM that have rheumatoid factor (RF) activity and bind to polyclonal immunoglobulins (usually IgGs)
 - Clinical
 - Typical triad: purpura, weakness, arthralgias
 - Multisystem organ involvement including chronic hepatitis, membranoproliferative glomerulonephritis, peripheral neuropathy due to leukocytoclastic vasculitis of small and medium-sized vessels
 - Proposed criteria for the classification of mixed cryoglobulinemia:
 - *Major*: serologies: mixed cryoglobulins, low C4; pathology: leukocytoclastic vasculitis
 - *Minor*: serologies: rheumatoid Factor +, HCV +, HBV +; pathology: clonal B cell infiltrates (liver-bone marrow)
 - ▲ "Definite" mixed cryoglobulinemia syndrome:

- △ Serum mixed cryoglobulins (\pm low C4) + purpura + leukocytoclastic vasculitis
 - △ Serum mixed cryoglobulins (\pm low C4) + 2 minor clinical symptoms + 2 minor serological/pathological findings
 - ▲ *"Incomplete" or "possible" mixed cryoglobulinemia syndrome:*
 - △ Mixed cryoglobulins or low C4 + 1 minor clinical symptom + 1 minor serological \pm pathological finding
 - △ Purpura and/or leukocytoclastic vasculitis + 1 minor clinical symptom + 1 minor serological \pm pathological finding
 - △ 2 minor clinical symptoms + 2 minor serological \pm pathological findings
 - ▲ *"Essential" or "secondary" mixed cryoglobulinemia syndrome*
 - ▲ Absence or presence of well known disorders (infections, immunological, neoplastic)
- Clinical findings
 - Palpable purpura (55% to 100%): higher in types II and III, intermittent, begin on legs
 - Raynaud's phenomenon: 33% of patients
 - Vasculitis: secondary to vascular deposition of circulating immunocomplexes
 - Arthralgias and arthritis in the proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, knees, and ankles (73%)
 - Renal immune-complex disease: 33% of patients, immunofluorescence demonstrates immunoglobulin and C3 deposits in the glomerulus (cryoglobulinemic glomerulonephritis)
 - Peripheral sensorimotor polyneuropathy with painful paresthesias, most commonly in types II and III
 - Systemic autoimmune disease: connective tissue diseases are seen in patients with types II and III; mainly primary Sjögren's syndrome and systemic lupus erythematosus
 - Liver involvement: high incidence of HCV in MC patients, increased enzymes, hepatomegaly, chronic hepatitis, steatosis, cirrhosis or hepatocellular carcinoma, liver failure leading to death (25%)
 - See Table 22-1 for clinical conditions that may be associated with cryoglobulinemia
 - Laboratory studies
 - Serum evaluation: specimen must be obtained in warm tubes (37°C)
 - Types I and II precipitate within the first 24 hours
 - Type III cryoglobulins may require 7 days
 - RF is positive in types II and III
 - Serum cryoglobulin values usually do not correlate with clinical severity and prognosis of the disease
 - Complement levels
 - Low complement levels are frequently observed in patients with cryoglobulinemia related to autoimmune disorders
 - Type II HCV related cryoglobulinemia presents with low levels of C4 and normal C3
 - Treatment
 - Treatment of the underlying disorder
 - Nonsteroidal anti-inflammatory drugs (NSAIDs)
 - Immunosuppressives: corticosteroid therapy and/or cyclophosphamide or azathioprine, interferon- α (IFN- α) and ribavirin for HCV-associated disease
 - Plasmapheresis with other immunosuppressive treatment: in patients with severe manifestations of MC
 - Rituximab: B-cell lymphoproliferative disorders and in autoimmune diseases

Cryofibrinogenemia

- Cryofibrinogen:
 - Precipitants of protein complexes made up of fibronectin, fibrinogen and fibrin
 - Found in the plasma but not in the serum of some individuals
 - Reversibly precipitates in cooled plasma at 4°C, and dissolves at 37°C
- Classification
 - Primary (essential)
 - Secondary and associated with
 - Carcinomas, infections, collagen-vascular diseases, thromboembolic diseases, cryoglobulins
- Clinical findings
 - Often clinically asymptomatic
 - Thrombotic vasculopathy characterized by: ischemia, purpura, livedo reticularis, ecchymosis, ulcers, necrosis and gangrene, purpura (77%)
 - Histology: fibrin thrombi within superficial dermal vessels
- Treatment
 - Usually unresponsive to treatment; may respond to fibrinolytic therapy

Seronegative Spondyloarthropathies

- Chronic inflammatory diseases of the joints associated with the HLA-B27 gene
- Characterised by shared rheumatic features including enthesitis, sacroiliitis, peripheral arthritis
- Also with associated extra-articular lesions notably psoriasis, uveitis, and inflammatory bowel disease
- Diseases
 - Ankylosing spondylitis/juvenile ankylosing spondylitis

TABLE 22-1 Clinical Conditions That May Be Associated With Cryoglobulinemia

Infections	
Viral	(Epstein-Barr virus, Cytomegalovirus, Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, HIV)
Bacterial	(Lyme disease, Syphilis, Lepromatous leprosy, Q fever, Poststreptococcal nephritis, Subacute bacterial endocarditis)
Fungal	(Coccidioidomycosis)
Parasitic	(Kala-azar Toxoplasmosis, Echinococcosis, Malaria, Schistosomiasis, Trypanosomiasis)
Hematologic Diseases	Autoimmune Diseases
Non-Hodgkin's lymphoma	Sjögren's syndrome
Hodgkin's lymphoma	Systemic lupus erythematosus
Chronic lymphocytic leukemia	Polyarteritis nodosa
Multiple myeloma	Systemic sclerosis
Chronic myeloid leukemia	Rheumatoid arthritis
Waldenström's macroglobulinemia	Autoimmune thyroiditis
Castleman disease	Temporal arteritis
Myelodysplasia	Dermatomyositis-polymyositis
Thrombocytopenic thrombotic purpura	Henoch-Schönlein disease
Cold agglutinin disease	Sarcoidosis
	Pulmonary fibrosis
	Biliary cirrhosis
	Primary antiphospholipid syndrome
	Inflammatory bowel disease
	Endomyocardial fibrosis
	Pemphigus vulgaris
From Tedeschi A, Baratè C, Minola E, Morra E. Cryoglobulinemia. Blood Rev. 2007 Jul;21(4):183–200.	

- Spondyloarthropathy of inflammatory bowel disease (IBD)
- Psoriatic arthritis
- Reactive arthritis (ReA)/Reiter syndrome (RS)
- Undifferentiated spondylarthropathy
- Ankylosing spondylitis
- Systemic rheumatic disorder of indeterminant etiology, (but with a strong genetic predisposition), and sacroiliac (SI) joint inflammation (sacroiliitis)
- HLA-B27: present in 95% of patients
- Reactive arthritis (ReA)
 - Previously called Reiter's syndrome
 - Aseptic inflammatory arthritis, triggered by infection at a distant site in genetically susceptible people

- Mainly affects patients 20–40 years old
 - Male to female ratio: 3:1
 - Human leukocyte antigen HLA-B27 (class one major histocompatibility complex gene)
 - Affects 45% to 90% of patients
 - Associated with more severe and prolonged disease, a higher prevalence of back pain, and are more likely to have mucocutaneous disease
 - HLA-B27 binds unique peptides of microbial or self origin and presents them to CD8 positive T cells causing specific immune responses
 - Usually follows gastrointestinal or genitourinary infections (Table 22-2)
 - Sporadic cases of sexually acquired reactive arthritis (SARA) is usually due to infection with *Chlamydia trachomatis*
 - Clinical findings
 - Acute episode of arthritis resolves spontaneously in 3–12 months
 - Reiter's syndrome (ACR definition):
 - Episode of peripheral arthritis of more than one month's duration occurring in association with urethritis or cervicitis
 - Musculoskeletal manifestations
 - ▲ Arthritis (95% of patients): acute, asymmetric, knees, ankles, feet
 - ▲ Spondylitis: low back pain radiating to buttocks or thighs
 - ▲ Entesitis: periarticular inflammation, can lead to "sausage digits"
 - Mucocutaneous involvement:
 - ▲ *Keratoderma blennorrhagica* (5% to 10% of patients): pustular psoriasis-like lesions on palms/soles, associated nail dystrophy
 - ▲ *Circinate balanitis/vulvitis*:
 - △ Painless gyrate white plaques eventually cover the entire surface of the glans penis
 - △ Painless shiny patches of the palate, tongue, and mucosa of the cheeks and lips
 - △ Psoriasiform dermatitis of elbows/knees/scalp
 - △ Pyoderma gangrenosum may also occur
 - Ocular involvement
 - ▲ Bilateral conjunctivitis (occurs in 30% of patients); also anterior uveitis
 - Genitourinary involvement
 - ▲ Urethritis or cervicitis: typically urethritis precedes conjunctivitis and arthritis
 - ▲ Dysuria
 - Gastrointestinal involvement
 - ▲ Enteric acquired reactive arthritis usually presents 4 weeks after infection
 - Renal involvement:
 - ▲ Immunoglobulin A (IgA) nephropathy
- Laboratory studies
 - Elevated ESR and CRP
 - Synovial fluid: leukocytosis; Gram stain/culture negative
 - Throat, stool, or urogenital tract cultures
 - Full blood count: neutrophilic leukocytosis, thrombocytosis, anemia of chronic disease
 - Synovial biopsy: polymorphous infiltrate indistinguishable from other chronic rheumatic diseases
 - Electrocardiogram: often normal but may show variable degrees of heart block

TABLE 22-2 Conditions to Which Arthritis May Be Reactive

	Probable	Possible
Respiratory infections		<i>Chlamydia pneumoniae</i> <i>Chlamydia psittaci</i> <i>Streptococcus pyogenes</i>
Genitourinary infections	<i>Chlamydia trachomatis</i>	<i>Mycoplasma fermentans</i> <i>Mycoplasma genitalium</i> <i>Neisseria gonorrhoeae</i> <i>Ureaplasma urealyticum</i>
Gastrointestinal infections	<i>Campylobacter jejuni</i> <i>Salmonella enteritidis</i> <i>Salmonella typhimurum</i> <i>Shigella flexneri</i> <i>Yersinia enterocolitica</i> <i>Yersinia pseudotuberculosis</i>	<i>Brucella abortus</i> <i>Clostridia difficile</i> <i>Cryptosporidium</i> <i>Entamoeba histolytica</i> <i>Escherichia coli</i> <i>Giardia lamblia</i>

- Treatment
 - Usually self-limited course, with resolution of symptoms by 3 to 12 months; 50% may have recurrent arthritis
 - Empiric treatment for *Chlamydia*
 - NSAIDs
 - Sulfasalazine, methotrexate, TNF- α -inhibitors

Psoriatic Arthritis (PsA)

- Found in 5% to 20% of patients with psoriasis; psoriasis precedes the onset of PsA in 60% to 80% of patients
- Occurs in 5% to 42% of patients with psoriatic skin disease (Ps)
- CASPAR (classification criteria for psoriatic arthritis) criteria for the classification of PsA (Table 22-3)
 - Specificity of 98.7% and sensitivity of 91.4%
- Clinical findings
 - *Asymmetric oligoarthritis*: 50% of male patients
 - Involvement of hands and feet; DIPs, PIPs, spares MCPs
 - Leads to “sausage digits”
 - *Symmetric polyarthritis*: most common pattern in women
 - RA-like pattern of hands, feet, ankles
 - Unlike RA, may involve the DIP, RF negative
 - *DIP joint*: “classic,” but uncommonly exclusively involved
 - *Arthritis mutilans*: least common variant
 - Severe, rapidly-progressive joint inflammation that results in digital shortening due to “telescoping” of digits and osteolysis (pencil in cup deformity on x-ray)
 - *Spondylitis and sacroiliitis*: axial arthritis, knees also involved, may have peripheral joint involvement, HLA-B26 positive
 - *Psoriatic-onychopachydermoperiostitis (POPP)*:
 - Psoriatic nail lesions
 - Soft tissue thickening above the terminal phalanx and radiologic involvement of the phalanx with periosteal reaction

- Laboratory studies
 - Elevated ESR and CRP
 - Leukocytosis of synovial fluid
 - Radiologic findings: x-ray—pencil-in-cup deformity, fluffy periosteal bone formation
- Treatment
 - NSAIDs
 - Methotrexate, sulfasalazine, and cyclosporine
 - TNF- α inhibitors: infliximab, etanercept, adalimumab

Scleredema (Scleredema Adultorum of Buschke, Scleredema Diabeticorum)

- Benign self-limited cutaneous mucinosis with irreversible glycosylation of collagen that is collagenase resistant
- Pathogenesis: unknown, hypotheses implicating immune mechanisms, direct action of bacterial toxin and effects of adrenal steroids released in response to infection
- 29% cases seen in children
- Type I: infection-association
 - Middle-aged women, preceding febrile illness, streptococcal, (tonsillitis, pharyngitis, and pyoderma), influenza, scarlet fever, measles, and mumps. Sudden-onset hardening of the cervicofacial region, with extension to the upper trunk and proximal extremities
 - Self-limited in several months
- Type II: monoclonal gammopathy-associated
 - Also associated with hyperparathyroidism, multiple myeloma, malignant insulinoma, rheumatoid arthritis, and Sjogren’s syndrome
 - Middle-aged women, no preceding illness
 - Similar course to type I
- Type III: diabetes and obesity associated
 - Middle-aged obese men
 - Slow-onset, persistent, erythema and induration of the posterior neck and back, peau d’orange
- Systemic findings
 - Serositis with possible pleural, pericardial and peritoneal effusions

TABLE 22-3 The CASPAR Criteria (Classification Criteria for Psoriatic Arthritis)

Requires the presence of inflammatory articular disease: (joint, spine, or enthesal)

Also presence of 3 points from the following 5 categories:

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis (first- or second-degree relative)
2. Typical psoriatic nail dystrophy: onycholysis, pitting, and hyperkeratosis
3. A negative test result for the presence of rheumatoid factor by any method except latex test
4. Either current dactylitis (swelling of an entire digit) or a history of dactylitis
5. Radiographic evidence of juxtaarticular new bone formation

- Dysarthria, dysphagia
- Myositis
- Parotitis
- Ocular abnormalities: trophic corneal disturbances
- Cardiac involvement: Wolff-Parkinson-White syndrome
- Histology: thickened dermis with deposition of mucin between thickened collagen bundles
- Treatment
 - Physical therapy
 - No known effective treatment

QUIZ

Questions

- The most specific antinuclear pattern for SLE is:
 - Rim
 - Speckled
 - Homogenous
 - Nucleolar
- Systemic lupus erythematosus is associated with:
 - HLA-DR4
 - HLA-DR2
 - HLA-DQ4
 - HLA-DQ2
- Which statement is TRUE about acute cutaneous lupus?
 - ACLE occurs in 80% to 90% of patients with SLE
 - ACLE tends to spare the nasolabial folds
 - ACLE flares with systemic disease
 - Alopecia is common in patients with ACLE
 - ACLE is the most photosensitive subtype of cutaneous lupus
 - B, C, and D
 - B, C, D, and E
 - All are true
- Which of the following is NOT an ACR criterion of SLE?
 - Complement deficiency
 - Arthritis
 - IgM anti-phospholipid antibody positivity
 - Oral ulcers
 - Positive lupus prep
 - Hemolytic anemia
 - A and C are not
 - A, C, and E are not
 - All of the above are criteria
- Which medication would NOT cause the following clinical scenarios?
 - Hydrochlorothiazide and a patient with SCLE, photosensitivity, arthritis, and a positive ANA in a speckled pattern
 - Griseofulvin and a patient with SCLE, photosensitivity, and a positive ANA in a speckled pattern
 - Phenytoin and a patient with a malar rash, photosensitivity, arthritis, pleurisy, and a positive ANA in a nucleolar pattern
 - Griseofulvin and a patient with a positive ANA in a homogenous pattern, arthritis, oral ulcers, hemolytic anemia, and pleurisy
 - Hydroxyurea and violaceous erythema over the knuckles, elbows, and knees, and a negative ANA
- Which of the following is TRUE?
 - The risk of malignancy in adults with dermatomyositis is 35–40%
 - Adults with dermatomyositis should have yearly malignancy screening for 2 years following their dermatomyositis diagnosis
 - The heliotrope eruption is the most common and characteristic cutaneous features of dermatomyositis
 - A patient with dermatomyositis with violaceous erythema on the elbows has Gottron's sign
 - Lipodystrophy, calcinosis cutis, and vasculopathic ulcers may occur in juvenile dermatomyositis
 - D and E are true
 - C, D, and E are true
- Scleroderma-like disorders can be seen in all of the following EXCEPT:
 - Stiff skin syndrome
 - Argyria
 - Crowe-Fukase syndrome
 - Vitamin K exposure
 - Isoniazid
- Which of the following statements about Shulman syndrome is FALSE?
 - Most cases have now been found to be associated with exposure to adulterated rapeseed oil
 - Fascial involvement leads to contractures and the "groove sign"
 - It is characterized by increased expression of genes for TGF- β in fibroblasts
 - It is usually steroid-responsive
 - 75% of cases have associated hypergammaglobulinemia

9. Which of the following is NOT associated with the listed type of cryoglobulinemia?
 - A. Rheumatoid factor positivity and type I cryoglobulinemia
 - B. Peripheral sensory polyneuropathy and type II cryoglobulinemia
 - C. Monoclonal IgG and type I cryoglobulinemia
 - D. Type I cryoglobulinemia and acrocyanosis
 - E. Cryoglobulinemic glomerulonephritis and type II cryoglobulins
10. Which of the following is NOT a feature of reactive arthritis?
 - A. Gyrate white plaques on the penis
 - B. Shiny patches on the palate
 - C. Anterior uveitis
 - D. Trachyonychia
 - E. IgA nephropathy

Answers

1. A. Although a homogenous pattern is also highly specific for SLE and is the most common pattern in SLE, rim is the most specific. Both are associated with anti-DNA antibodies and antibodies to histone.
2. B. SLE is associated with HLA DR2 and DR3.
3. F. Localized ACLE (malar rash) occurs in only 20% to 60% of patients with SLE, spares the nasolabial folds (unlike dermatomyositis), flares with systemic disease, and is often associated with alopecia (telogen effluvium-like). Although it is quite photosensitive, it is less so than SCLE.
4. A. Complement deficiency is the only item that is not an ACR criterion for SLE.
5. C. Phenytoin can cause drug-induced SLE, but cutaneous manifestations are usually not present, and the ANA pattern is rim or homogeneous, corresponding with anti-histone antibodies. Hydrochlorothiazide is a common cause of drug-induced SCLE, and can be associated with mild systemic symptoms and a positive Ro or La antibody. Griseofulvin can cause both drug-induced SLE (associated with anti-histone antibodies and usually without cutaneous involvement) and drug-induced SCLE (associated with anti-Ro/La Abs). Hydroxyurea is associated with cutaneous findings consistent with dermatomyositis, with no associated evidence of muscle weakness, and usually with a negative ANA.
6. F. It is true that patients with violaceous erythema of the elbows have Gottron's sign and that lipodystrophy, calcinosis cutis and vasculopathic ulcers are possible complications of juvenile DM. The risk of malignancy in adults with DM is in fact 20% to 25%, and the risk remains elevated for at least 3–5 years, so that malignancy surveillance should be done annually for that period of time (perhaps longer). The most common lesion in DM is in the fact the Gottron's papule, not the heliotrope eruption.
7. B. A scleroderma-like disorder is not seen with argyria. Acrogeria, which sounds like argyria, is a premature aging syndrome that can be associated with scleroderma-like changes. Crowe-Fukase syndrome is another name for POEMS syndrome.
8. A. Toxic oil syndrome, which can present similarly to eosinophilic fasciitis, is associated with adulterated rapeseed oil exposure. However, it is a very small subset of patients with the clinical presentation. The other items are true.
9. A. Rheumatoid factor positivity is seen in types II and III cryoglobulinemia. The remaining associations are correct.
10. D. Trachyonychia is not commonly seen in patients with reactive arthritis (previously known as Reiter's syndrome).

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CUTANEOUS MANIFESTATIONS OF METABOLIC DISEASES

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PORPHYRIAS

- Metabolic disorders of heme synthesis; may be hereditary or acquired
- Photosensitivity due to exposure of ultraviolet (UV) radiation in the Soret band (400 to 410 nm)

Classification of Porphyrrias: Erythropoietic and Hepatic Forms (Based on the Primary Site of Expression of the Enzymatic Defect)

- Non-acute porphyrias: porphyria cutanea tarda (PCT), erythropoietic porphyria (EPP), congenital erythropoietic porphyria (CEP) and hepatoerythropoietic porphyria (HEP); most common cutaneous manifestation is photosensitivity
- Acute porphyrias: acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP) and ALA dehydratase deficiency porphyria (plumboporphyria)
- Heme biosynthesis:
 - Major sites of heme synthesis are bone marrow (85%) and in the liver
 - Initial reaction takes place in the mitochondrion within the cell
 - Condensation of 1-glycine and 1-succinylCoA by Δ -aminolevulinic acid synthase (ALA synthase): rate-limiting reaction of heme biosynthesis
 - Mitochondrial Δ -aminolevulinic acid (ALA) is transported to the cytosol
 - ALA dehydratase (also called *porphobilinogen synthase*) dimerizes two molecules of ALA to produce porphobilinogen

- Uroporphyrinogen I synthase, also called *porphobilinogen deaminase* or *PBG deaminase*, causes condensation of four molecules of porphobilinogen to produce intermediate hydroxymethylbilane
- Hydroxymethylbilane undergoes enzymatic conversion to uroporphyrinogen III by uroporphyrinogen synthase plus a protein known as *uroporphyrinogen III cosynthase*
- In the cytosol, the acetate substituents of uroporphyrinogen (normal uroporphyrinogen III or abnormal uroporphyrinogen I) are decarboxylated by uroporphyrinogen decarboxylase
- The resulting coproporphyrinogen III intermediate is transported to the interior of the mitochondrion, where, after decarboxylation, protoporphyrinogen IX results
- In the mitochondrion, protoporphyrinogen IX is converted to protoporphyrin IX by protoporphyrinogen IX oxidase
- Final reaction in heme synthesis takes place in the mitochondrion by ferrochelatase

ERYTHROPOIETIC PORPHYRIAS

Congenital Erythropoietic Porphyria (EP)

GUNTHER DISEASE

- Autosomal recessive with complete absence of UROS gene activity; affects uroporphyrinogen III synthase and the production of uroporphyrinogen III

- Results in massive accumulation and excretion of uroporphyrin I and coproporphyrin I
- Clinical findings
 - Appears soon after birth
 - *Cutaneous*:
 - Severe photosensitivity with burning, edema, bullae, mutilating scars, loss of brows/lashes, hypertrichosis, hyper/hypopigmentation
 - Ocular: photophobia, kerato conjunctivitis, ectropion, symblepharon, loss of vision
 - *Other*: gallstones possible, cartilaginous breakdown, red/brown urine, erythrodontia (seen with Wood's lamp), splenomegaly, hemolytic anemia
- Laboratory findings
 - *Urine*: uroporphyrin I, coproporphyrin I
 - *Stool*: coproporphyrin I
 - *Blood*: plasma-uroporphyrin I, coproporphyrin I; RBC: uroporphyrin I, coproporphyrin and some protoporphyrin
- Other diagnostic tests: urine fluoresces reddish pink
- Treatment: strict photoprotection, splenectomy, blood transfusions, activated charcoal, hydroxyruea

Erythropoietic Protoporphyrria (EPP)

- Autosomal dominant
- *FECH* gene mutation results in partial ferrochelatase deficiency
- Most common erythropoietic porphyria
- Clinical findings
 - *Cutaneous*: photosensitivity: painful erythematous, edematous plaques after exposure to UV light that may heal with scarring, skin lichenification, leathery pseudovesicles, nail changes
 - *Hepatic*: porphyrin gallstones (early age), liver disease (10% of patients): jaundice, cirrhosis
- Laboratory findings
 - *Urine*: normal
 - *Stool*: protoporphyrin
 - *Blood*: RBC/plasma: protoporphyrin
- Treatment: photoprotection, beta-carotene (synthetic), red blood cell transfusions, cholestyramine, activated charcoal
- Prognosis: normal life span if liver spared

CHRONIC HEPATIC PORPHYRIA

Porphyria Cutanea Tarda (PCT) (Fig. 23-1)

- Autosomal dominant
- Uroporphyrinogen decarboxylase (UROD) deficiency in the liver



FIGURE 23-1 Porphyria cutanea tarda. (Reproduced with permission from Wolff et al: *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- Three types: Type I: decreased hepatic UROD activity, but normal erythrocyte UROD activity (sporadic fashion); Type II: decreased UROD activity in red cells and in the liver (occurs in multiples in a family); Type III decreased hepatic UROD activity and normal erythrocyte activity (occurs in multiples in a family)
- Most common of the porphyrias
- Clinical findings
 - *Cutaneous*: chronic bullae, vesicles and erosions on sun-exposed skin, bullae and vesicles rupture easily, hypertrichosis, milia, sclerodermoid changes
 - *Hepatic*: associated with hepatitis C, hepatocellular carcinoma, increased liver iron stores
 - *Other*: HIV (human immunodeficiency virus) infection, dermatomyositis
- Laboratory findings
 - *Urine*: uroporphyrin I-III > coproporphyrin; coral-pink fluorescence of urine under Wood's lamp
 - *Stool*: isocoproporphyrins, tetracarboxyl porphyrins, protoporphyrin
 - *Blood*: RBC normal; plasma: increased uroporphyrin
 - *Serum iron*: increased
 - *Liver biopsy*: hepatocellular damage with fatty infiltration and hemosiderosis
- Treatment: photoprotection, phlebotomy (until serum transferrin saturation and serum ferritin levels are normalized), antimalarials (hydroxychloroquine)

or chloroquine); recombinant erythropoietin for end stage renal disease patients, avoidance of alcohol, estrogen, iron supplements

- Interferon for hepatitis C

Hepatoerythropoietic Porphyria (HEP)

- Autosomal dominant
- Homozygous or compound heterozygous deficiency of uroporphyrinogen decarboxylase (UROD) deficiency
- Clinical findings
 - Resembles CEP, severe photophotosensitivity with burning, erythema, vesicles, bullae, mutilating scar formation, hypertrichosis, sclerodermoid skin changes
 - Other: hemolytic anemia, splenomegaly, dark urine at birth
- Laboratory findings
 - *Urine*: uroporphyrin I–III, isocoproporphyrin
 - *Stool*: uroporphyrin, coproporphyrin, isocoproporphyrin
 - *Blood*: RBC: protoporphyrin, plasma: uroporphyrin
- Treatment: photoprotection, red cell transfusion, hydroxyurea
- Prognosis: normal lifespan

ACUTE HEPATIC PORPHYRIAS

Acute Intermittent Porphyria (AIP)

- Autosomal dominant
- Mutation of porphobilinogen deaminase (PBGD) gene leading to deficient activity of the enzyme
- More common in women than in men
- Attacks may be precipitated by drugs (barbiturates, sulphonamides), hormones, fever, smoking, infections, surgery, stress, or starvation
- Clinical findings
 - *Cutaneous*: no skin findings
 - *Neurologic*: neuropathy, palsy, seizures, coma
 - *Psychiatric*: confusion
 - *Hyponatremia*: common during acute attacks, due to inappropriate release of antidiuretic hormone
 - *Other*: abdominal pain, risk of hepatic carcinoma
- Laboratory findings
 - Erythrocyte PBG deaminase activity: reduced in type I and type III AIP patients; Type II AIP patients show normal PBGD activity in erythrocytes, but have reduced PBGD activity in non-erythroid cells
 - *Urine*: latent: aminolevulinic acid (ALA) and porphobilinogen (PBG); acute: ALA, PBG, uroporphyrin, coproporphyrin
 - *Stool*: normal
 - *Blood*: normal

- Treatment: avoid precipitators, IV glucose loading and hematin infusions during attacks; supportive care
- Prognosis: acute attacks may be life-threatening and leave residual neurologic deficits

Variegate Porphyria (VP)

- Autosomal dominant
- Protoporphyrinogen oxidase (PPO) deficiency
- Mixed porphyria: can present with neurological manifestations, cutaneous photosensitivity, or both
- Most common in South Africans
- Clinical findings
 - Skin lesions similar to PCT: fragility of skin, vesicles, bullae, erosions, milia, hyperpigmentation, hypertrichosis, and photosensitivity
 - Symptoms similar to AIP: abdominal pain, tachycardia, vomiting, constipation, hypertension, neuropathy, back pain, confusion, bulbar paralysis, psychiatric symptoms, fever, urinary frequency, dysuria, hyponatremia
 - Attacks may be precipitated by alcohol, hormones, and drugs (dapsone, anticonvulsants, barbiturates, sulfonamides, griseofulvin)
- Laboratory findings
 - *Urine*: ALA, PBG, uroporphyrin elevated during attacks; coproporphyrin > protoporphyrin (acute and asymptomatic periods: helps distinguish from PCT)
 - *Stool*: protoporphyrin and coproporphyrin elevated
 - *Blood*: presence of plasma porphyrin (fluoresces at 626 nm)
 - *Biliary porphyrins*: increased risk of gallstones in VP, consist mainly of protoporphyrin
- Treatment: avoid precipitators, photoprotection
 - Treat acute attacks similar to AIP

Hereditary Coproporphria (HCP)

- Autosomal dominant
- Coproporphyrinogen oxidase (CPO) deficiency
- Exacerbated by: barbiturates, endogenous or exogenous steroid hormones
- Clinical findings:
 - Similar to AIP and VP, with gastrointestinal and neurologic attacks
 - *Cutaneous*: photosensitive bullae (30% of patients), hypertrichosis
 - Other: hemolytic anemia beginning in childhood, increased risk of hepatocellular carcinoma
- Laboratory findings
 - *Urine*: coproporphyrin III; ALA, PBG, and uroporphyrin also increased during attacks
 - *Stool*: coproporphyrin III
 - *Blood*: normal

- Treatment: avoid precipitators, photoprotection
 - Treat acute attacks as with AIP

ALA Dehydratase Porphyrria (ADP)

- Autosomal recessive
- ALA dehydratase deficiency
- Due to ALAD mutations
- Clinical findings
 - No skin lesions
 - Symptoms similar to AIP
- Laboratory findings
 - *Urine*: ALA, coproporphyrin, uroporphyrin
 - *Stool*: coproporphyrin, protoporphyrin
 - *Blood*: protoporphyrin
 - Treatment: avoid offending agent: such as alcohol and stress, intravenous infusion of glucose

SPHINGOLIPIDOSES (LIPID STORAGE DISORDERS)

- Diseases caused by defects in genes encoding proteins involved in the lysosomal degradation of sphingolipids
- Leads to lysosomal accumulation of the enzyme's specific sphingolipid substrate
- Diseases are named according to the identity of the storage material
- Mode of inheritance is autosomal recessive except for Fabry's disease (X-linked recessive)

Fabry Disease (Angiokeratoma Corporis Diffusum)

- X-linked recessive, Xq22
- Defective lysosomal α -galactosidase A
- Results in accumulation and deposition of glycosphingolipids (globotriaosylceramide) in plasma and lysosomes of vascular endothelial and smooth muscle cells
- Presents in adolescence
- Clinical findings
 - *Ocular*: corneal and lenticular opacities
 - *Vascular*: ischemia, coronary artery disease, cerebrovascular accident (CVA), peripheral neuropathy
 - *Cutaneous*: angiokeratomas of lower trunk, thighs, oral/ocular mucosa (Fig. 23-2)
 - *Renal*: failure
 - *Genitourinary*: maltese crosses in urine: lipid inclusions with characteristic birefringence
 - *Other*: painful crises, acroparesthesias, hypohidrosis
- Treatment: enzyme replacement therapy arrests progression of disorder, dialysis, symptomatic pain management, phenytoin and carbamazepine for paresthesias

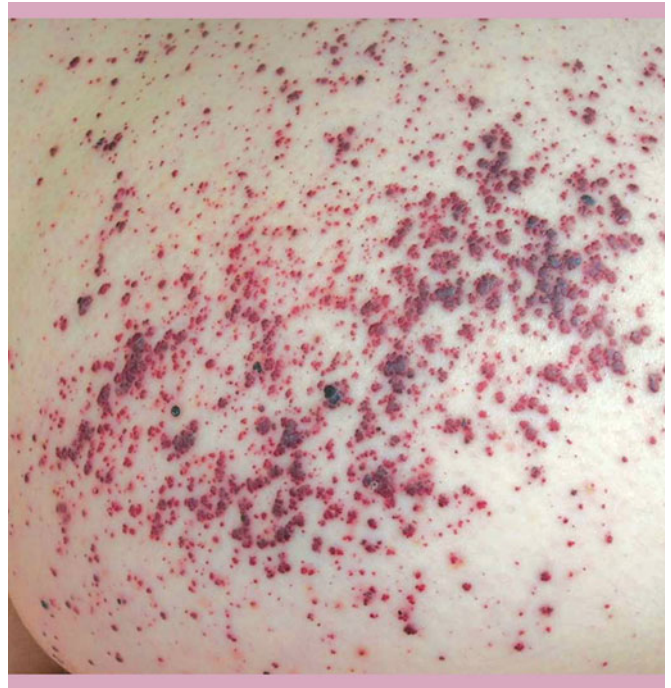


FIGURE 23-2 Angiokeratomas. (Reproduced with permission from Wolff et al: *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- Prognosis: death by fifth decade from myocardial infarction, CVA, and renal failure

Gaucher Disease

- Autosomal recessive
- Decreased glucosylceramide- β -glucocerebrosidase activity with resulting accumulation of glucocerebroside in histiocytes (Gaucher cells)
- Most common form of sphingolipidoses
- Clinical findings
 - *Type I* (adult): attenuated form; diffuse hyperpigmentation, petechiae, ecchymoses, bone pain, fractures, aseptic necrosis of femoral head, hepatosplenomegaly, lymphadenopathy, pinguiculae, pancytopenia
 - *Type II* (infantile): acute form; CNS involved with hypertonicity, neck rigidity, laryngeal spasm, dysphagia, hepatosplenomegaly, aspiration pneumonia, subset with severe congenital ichthyosis and collodion membrane
 - *Type III*: (juvenile) subacute form; intermediate variant of types I and II
- Laboratory studies
 - Gaucher cell in the reticuloendothelial system: macrophages are enlarged with cytoplasmic inclusions
 - Elevated glucosylceramide in plasma
 - X-ray: erlenmeyer flask deformity of the distal femur

- Treatment
 - *Type I*: imiglucerase (Cerezyme), a recombinant-derived analogue of β -glucocerebrosidase; bone marrow transplant, splenectomy
 - *Type II*: supportive care, antibiotics (enzyme replacement is unable to cross blood-brain barrier); death at 1 to 2 years owing to aspiration
 - *Type III*: bone marrow or stem cell transplants

Niemann-Pick Disease (NPD)

- Autosomal recessive (SMPD1)
- High incidence in Ashkenazi Jews
- Three types:
 - Types A and B due to acid sphingomyelinase (ASM) deficiency with sphingomyelin accumulation (foam cells)
 - Type C is due to NPC-1 or NPC-2 gene deficiency
 - Secondary drug induced degradation of acid sphingomyelinase results in lysosomal storage of sphingomyelin; occurs secondary to tricyclic antidepressants
- Clinical findings
 - Type A (most common): xanthomas, psychomotor deterioration, hepatosplenomegaly, failure to thrive, lymphadenopathy, blindness, cherry red spots in fovea, deafness, pneumonia
 - Type B: central nervous system spared, pulmonary infiltration, hepatosplenomegaly
 - Type C: developmental delay, psychomotor deterioration, hepatosplenomegaly; cholesterol esterification defect (normal sphingomyelinase)
- Laboratory studies: Niemann-Pick cells: lipid-laden foam cells
- Prognosis:
 - *Type A*: death by 2 to 3 years with failure to thrive, pneumonia
 - *Type B*: death in adolescence or adulthood; treatment with bone marrow transplant
 - *Type C*: death in adolescence

Fucosidosis

- Autosomal recessive
- Mutations of the FUCA 1 gene on chromosome 1p34 results in alpha-L-fucosidase deficiency: abnormal accumulations of glycosphingolipids, glycolipids, and glycoproteins (fucose-containing compounds)
- Clinical findings
 - Type I: neurologic changes, cardiomegaly, severe mental retardation, respiratory tract infections, hyperhidrosis, dysostosis multiplex, elevated sweat chloride, seizures
 - Type II: late infantile onset, short stature, coarse facies, mental retardation, hypertonemia; chloride

normal, angiokeratomas (similar distribution to Fabry's disease), longer survival than type I

- Treatment: laser therapy for angiokeratomas

Farber (Acid Ceramidase Deficiency, Lipogranulomatosis)

- Autosomal recessive
- Deficiency of lysosomal acid ceramidase and storage of ceramide in the lysosomes
- Clinical findings
 - *Skeletal*: painful and progressive joint deformations, periarticular swelling
 - *Cutaneous*: subcutaneous nodules (lipogranulomas)
 - *Ocular*: mild macular degeneration
 - *Pulmonary* failure
 - *Other*: progressive hoarseness, mental retardation
- Treatment: bone marrow transplantation, which improves the peripheral, but not the neurological manifestations

Mucopolysaccharidoses (MPS) (Lysosomal Storage Diseases)

- Inherited deficiency of enzymes that are involved in the degradation of glycosaminoglycans (GAGs); also referred to as *acid mucopolysaccharides* (Table 23-1)
- Dermatan sulfate, heparan sulfate, keratan sulfate (KS), and chondroitin sulfate are the main GAGs in tissues composed of sulfated sugar and uronic acid residues (except for KS)
- Diseases are autosomal recessive, except for MPS type II (Hunter), which is X-linked recessive

Hurler Syndrome (MPS-IH, Gargoylism)

- Autosomal recessive
- Defect in alpha-L-iduronidase, resulting in dermatan, heparan sulfate accumulation
- Classic form of MPS
- Clinical findings
 - Coarse facies with macrocephaly, hypertelorism, hirsutism, valvular disease, umbilical hernias, upper respiratory infections, corneal opacities, short stature, dysostosis multiplex
- Scheie MPS-IS: mild form of the MPS-IH, onset at 5 or 6 years, aortic valve disease, joint stiffness, claw hands, deformed feet, genu valgum, deafness, corneal clouding, normal intelligence and life span
- Scheie and Hurler compound syndromes (MPS-IH/S): clinically intermediate between types IH and IS, healthy at birth; onset of symptoms at 3 to 8 years, corneal clouding, joint stiffness, dysostosis multiplex, and heart disease
- Course: deaths caused by upper airway obstruction and pulmonary complications

TABLE 23-1 Mucopolysaccharidoses (MPS)

Number	Syndrome Name	Enzyme Deficiency	Glycosaminoglycan Stored
MPS I (severe)	Hurler	α -L-iduronidase	Dermatan sulfate, heparan sulfate
MPS I (attenuated)	Scheie	α -L-iduronidase	Dermatan sulfate, heparan sulfate
MPS I (attenuated)	Hurler-Scheie	α -L-iduronidase	Dermatan sulfate, heparan sulfate
MPS II (severe)	Hunter (severe)	Iduronate sulfatase	Dermatan sulfate, heparan sulfate
MPS II (attenuated)	Hunter (mild)	Iduronate sulfatase	Dermatan sulfate, heparan sulfate
MPS IIIA	Sanfilippo A	Heparan N-sulfatase	Heparan sulfate
MPS III B	Sanfilippo B	α -N-acetyl-glucosaminidase	Heparan sulfate
MPS III C	Sanfilippo C	Acetyl CoA: α -glucosaminide acetyltransferase	Heparan sulfate
MPS III D	Sanfilippo D	N-acetylglucosamine sulfatase	Heparan sulfate
MPS IV A	Morquio, type A	Galactose-6-sulfatase	Keratan sulfate, chondroitin 6-sulfate
MPS IV B	Morquio, type B	β -glactosidase	Keratan sulfate
MPS VI	Maroteaux-Lamy	N-acetylgalactosamine 4-sulfatase (arylsulfatase B)	Dermatan sulfate
MPS VI	Sly	B-glucuronidase	Dermatan sulfate, heparin sulfate, chondroitin 4-, 6 sulfates
MPS IX		Hyaluronidase	Hyaluronan

- Treatment
 - Bone marrow transplantation for Hurler's syndrome (not helpful for Hunter)
 - Laronidase: increases catabolism of glycosaminoglycans (GAGs)
 - Corrective surgery for joint contractures; corneal transplants, valve replacement

Hunter Syndrome (MPS II)

- X-linked recessive
- Defect of iduronate 2-sulfatase
- Accumulation of heparan and dermatan sulfate
- Clinical findings
 - Type A: severe form, clinical features similar to MPS-IH

- *Cutaneous*: ivory papules distributed symmetrically between the angles of the scapulae and posterior axillary lines; marker for the disease, hypertrichosis may result in synophrys
- *Ocular*: atypical retinitis pigmentosa
- Type B: mild form, clinical features similar to MPS-IS, airway obstruction secondary to accumulation of mucopolysaccharide in the trachea and bronchi, deafness
- Treatment: symptomatic care; enzyme replacement

Sanfilippo Syndrome (MPS Type III)

- Heparan-N-sulfatase deficiency
- Accumulation of heparan sulfate

- Clinical findings
 - Regression of psychomotor development
 - Neurologic: hyperactivity, autistic features, behavioral disorder

Morquio Syndrome (MPS Type IVA)

- N-acetylgalactosamine-6-sulfatase deficiency
- Accumulation of keratan sulfate and chondroitin-6-sulfate
- Clinical findings
 - *Skeletal*: kyphoscoliosis, pectus carinatum, subluxation of the hips
 - Aortic valvular disease
 - Dental abnormalities: odontoid hyperplasia

Morquio Syndrome, Type B (MPS Type IVB)

- β -Galactosidase deficiency
- Accumulation of chondroitin-6-sulfate

Maroteaux-Lamy Syndrome (MPS Type VI)

- Arylsulfatase B (N-acetyl glucosamine 4 sulfatase) with accumulation of dermatan sulfate
- Clinical findings
 - First clinical signs usually appear in the first 2 years of life, psychomotor retardation, clinically resembles Hurler's syndrome
- Treatment: galsulfase enzyme replacement

Sly Syndrome (MPS Type VII)

- β -glucuronidase deficiency
- Clinical findings: facial deformities: hypertelorism, prominent maxilla, depressed bridge of the nose; hydrops fetalis in neonatal form, hepatosplenomegaly
- Diagnosis: mucopolysaccharide staining:
 - *Acid*: hematoxylin and eosin, Giemsa, colloidal iron mucicarmine, Alcian blue, pH 2.5, methyl and toluidine blue
 - *Neutral*: periodic acid Schiff, gamori methinamine silver
 - *Sulfated*: aldehyde fuschin, Alcian blue, pH 0.5

DISORDERS OF AMINO ACID METABOLISM

Alkaptonuria/Ochronosis

- Autosomal recessive, chromosome 3q
- Deficient homogentisic acid oxidase (HGA), intermediate product of phenylalanine and tyrosine breakdown; excessive amounts of HGA are excreted in the urine and turn into a brown pigment on exposure to air causing the urine to appear dark
- Ochronosis is the connective tissue manifestation of alkaptonuria

- In the body, polymerized HGA accumulates in connective tissues, such as the skin and cartilage resulting in pigmentation and degeneration
- HGA inhibits enzymes that are needed for the cross-linking of collagen fibers, which can result in degeneration of cartilage resulting in arthralgias
- *Exogenous ochronosis*: caused by medications such as quinacrine, carbolic acid, hydroquinone, phenol, resorcinol, picric acid, and antimalarials; metabolism of these medications results in an HGA polymer like substance that differs from the polymer found in alkaptonuria
- Clinical findings
 - *Cutaneous*: macular blue-gray pigmentation on face, sclera, pinna, nasal ala, papules, milia, and nodules
 - *Skeletal*: narrowing of the joint spaces and disc calcifications, large joint arthropathy
 - *Cardiac*: cardiac valve calcification, stenosis, coronary artery calcification
 - *Renal*: stones
 - *Other*: black cerumen and sweat, dark urine at pH > 7
 - *Exogenous ochronosis*: no joint involvement
- Diagnosis:
 - Urinary homogentisic acid level
 - Darkening of urine with NaOH
 - *Histology*: ochronotic (yellow-brown) pigment in dermis, "yellow bananas," and within macrophages, homogenization and swelling of collagen bundles
 - Magnetic resonance imaging: thickened tendons, asymptomatic tears
 - Echocardiogram and CT: coronary artery calcifications and cardiac valve defects
 - Ultrasound and x-ray: renal stones
- Treatment
 - Arthritis: analgesics, physical therapy
 - Supplemental vitamin C
 - Nitisinone (inhibits homogentisic acid production)
 - Pigment changes persist

Phenylketonuria (PKU)

- Autosomal recessive
- Chromosome arm 12q
- Presents at birth
- Deficiency of phenylalanine hydroxylase, cofactor required for hydroxylation of tyrosine (a precursor of dopamine) and hydroxylation of tryptophan (a precursor of serotonin)
- Clinical findings
 - Toxic CNS effects
 - Mental retardation, seizures, hyperreflexia, microcephaly, brain calcification, cataracts

- *Cutaneous*: generalized hypopigmentation, blond hair, blue eyes; due to tyrosine deficiency, eczema, sclerodermoid skin (spares hands and feet), photosensitivity
- Urine and sweat has “mousy” odor (due to phenylacetic acid)
- Diagnosis: check for serum elevation of phenylalanine, neonatal screening, elevated urinary phenylpyruvic acid level
- Treatment: begin low-phenylalanine diet early to prevent CNS and skin changes; supplemental tyrosine, supplemental tetrahydrobiopterin
- Course: Normal life span if treated early

Homocystinuria

- Autosomal recessive
- Cystathionine β -synthetase deficiency, results in defect of methionine metabolism, and accumulation of homocystine
- Competitive inhibitor of tyrosinase
- Presents in early childhood
- Clinical findings
 - *Cutaneous*: malar flush, livedo reticularis, pale and pink skin: due to tyrosine deficiency, buccal skin shows red macules, hyperhidrosis, xerosis, and acrocyanosis, leg ulcers
 - Ocular: ectopia lentis with downward displacement, glaucoma
 - Vascular: cerebrovascular occlusions, deep venous thrombosis
 - Other: mental retardation, seizures, Marfanoid habitus
- Treatment: low methionine, high-cystine diet, pyridoxine (300 to 600 mg/day), folic acid, betaine, cyanocobalamin
- Course: death in third to fourth decade from vascular events

Richner-Hanhart Syndrome (Tyrosinemia II)

- Autosomal recessive
- Hepatic tyrosine aminotransferase (TAT) deficiency
- Tyrosinemia types I and III do not have skin involvement
- Clinical findings
 - *Ocular*: herpetiform corneal ulcers, photophobia, corneal clouding with central opacities, neovascularization, blindness
 - *Cutaneous*: focal or diffuse yellowish palmoplantar keratoderma, lesions associated with hyperhidrosis, erosions, bullae, hyperkeratotic plaques on elbows, knees in older patients
 - Other: mental retardation, seizures, self mutilation
- Diagnosis: plasma amino acid and urine organic acid levels of tyrosine are elevated; urinary tyrosine metabolite levels are elevated

- Treatment: topical therapy, oral retinoids, low-phenylalanine/tyrosine diet can prevent skin and eye manifestations

DEPOSITION DISORDERS

Lipoid Proteinosis (Urbach-Wiethe Disease, Hyalinosis Cutis et Mucosae)

- Autosomal recessive
- Defect in extracellular matrix protein 1 (encoded by the *ECM1* gene); ECM1 is known to inhibit bone mineralization, contribute to epidermal differentiation, and stimulate angiogenesis
- Accumulation of eosinophilic material composed of mucopolysaccharides, hyaluronic acid, neutral fat, lipids, and cholesterol
- Clinical findings
 - *Cutaneous*: patchy areas of alopecia may develop where hyaline deposits are present, early bullae formation on the face and distal extremities that heal with ice-pick scarring, infiltrated nodules on elbows, knees, and hands, skin becomes waxy, thickened, and yellow, beaded papules along the eyelid margins (moniliform blepharosis) (Fig. 23-3)
 - *Oral cavity*: cobblestone appearance to mucosa due to infiltrative papules on mucous membranes, large “wooden” tongue, parotiditis, dental anomalies
 - *Neurologic*: psychiatric symptoms due to calcification of the temporal lobes
 - *Earliest sign*: hoarse cry due to vocal cord infiltration and possible airway compromise

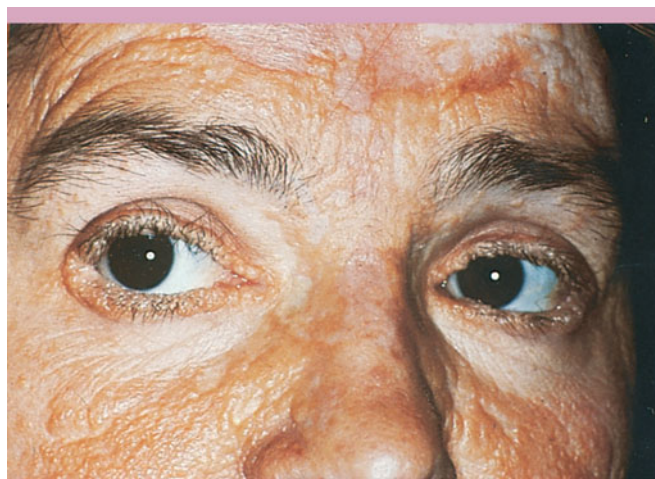


FIGURE 23-3 Lipoid proteinosis. (Reproduced with permission from Wolff et al: *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- Diagnosis: CT or x-ray: hippocampal “bean-shaped” calcifications
- *Histology*: deposition of amorphous eosinophilic material at the dermal-epidermal junction, perivascularly and along adnexal epithelia. Hyaline material, PAS (+) and diastase resistant found perpendicular to the basement membrane. Arranged in “onion skin” layers around blood vessels; cytoplasmic vacuoles in dermal fibroblasts
- Treatment: oral dimethylsulfoxide, retinoids may be helpful, CO₂ laser for skin lesions, vocal cord lesions and eyelid papules
- Course: chronic course

Wilson Disease (Hepatolenticular Degeneration)

- Autosomal recessive
- Defect of *ATP7B* gene: copper-transporting adenosine triphosphatase (ATPase) in the liver
- Excessive absorption of copper from the small intestine
- Decreased excretion of copper by the liver; decreased serum ceruloplasmin and increased copper in the liver
- Seen in childhood to adulthood
- Diagnostic criteria: seven criteria, including; (1) presence of Kayser-Fleischer (KS) rings; (2) typical neurological symptoms; (3) decreased serum ceruloplasmin concentration; (4) Coombs’ negative hemolytic anemia; (5) elevated urinary copper excretion; (6) high liver copper value in the absence of cholestasis; and (7) mutational findings
- Clinical findings
 - Copper accumulates in liver, brain, and cornea
 - *Hepatic*: hepatomegaly, cirrhosis
 - *Ocular*: Kayser-Fleischer ring: deposition of copper in Descemet membrane of cornea
 - *Cutaneous*: pretibial hyperpigmentation, blue lunulae, jaundice, varices, spider angiomas, and palmar erythema
 - *Other*: dysarthria, ataxia, dementia
- Diagnosis: low serum ceruloplasmin (copper carrier) levels, total serum copper levels are low and serum free-copper levels are elevated
- Treatment:
 - D-Penicillamine (risk of EPS), copper chelators, liver transplant, decreased copper intake
 - Symptoms reverse (except CNS) with early treatment

Hemochromatosis

- Autosomal recessive
- Mutations in the *HFE* gene; chromosome 6
- Hereditary hemochromatosis (HH) comprises a group of inherited disorders of iron metabolism

that can result in progressive iron overload, morbidity, and mortality

- Increased iron absorption with solid-organ iron deposition
- Presents in fifth decade
- Clinical findings
 - *Cutaneous*: diffuse gray hyperpigmentation, sparse hair, koilonychia
 - *Hepatic*: hepatomegaly, cirrhosis, fibrosis, hepatocellular carcinoma
 - *Cardiac*: cardiac failure, arrhythmias
 - *Other*: diabetes, hypogonadism, polyarthritides
- Diagnosis: fasting serum transferrin saturation and ferritin levels elevated, serum iron levels increased, liver biopsy (fibrosis, cirrhosis)
- Treatment: serial phlebotomy, deferoxamine, supportive care of diabetes, arrhythmias
- Course: premature death owing to hepatic failure, hepatocellular carcinoma, heart disease

Amyloidosis

- Insoluble protein (misfolded plasma protein) fibrils accumulate extracellularly
- Up to 24 different proteins have been recognized; all share a common core structure that consists of a cross β core and polypeptide chains (Table 23-2)
- Diagnosis
 - Typing of systemic amyloidoses with refined immunohistochemical analysis and genetic testing
 - Systemic amyloidosis: histologic demonstration of amyloidosis within an organ; in AL amyloidosis fine needle aspiration of abdominal fat can substitute for histological demonstration of amyloidosis
- Histology: eosinophilic, amorphous, fissured masses of amyloid in dermis and subcutaneous tissue, extravasated red blood cells, no lymph, intradermal bullae around blood vessels; amyloid rings (amyloid around individual fat cells)
- Stains:
 - Congo red (brick red, apple-green birefringence)
 - Crystal violet (metachromasia [red])
 - Methyl violet (metachromasia)
 - PAS+ and diastase-resistant
 - Indirect immunofluorescence: differentiates AA/AL
 - Bone marrow: 10% plasma cells (40% of patients)
 - Bence-Jones protein: monoclonal Ig light chain 90% in serum or urine
- Immunoelectrophoresis: monoclonal protein
- Electron microscopy: regular fibrillar structure
- X-ray diffraction: β -pleated sheet structure

TABLE 23-2 Classification of Amyloidoses

Amyloid Protein	Precursor	Systemic (S) or Localized (L)	Syndrome or Involved Tissue
AL	Immunoglobulin light chain	S, L	Primary
			Myeloma-associated
AH	Immunoglobulin heavy chain	S, L	Primary
			Myeloma-associated
			Familial
ATTR	Transthyretin	S	Senile systemic
A β_2 M	β_2 -microglobulin	S	Hemodialysis
AA	(Apo)serum AA	S	Secondary, reactive
AApoA-I	Apolipoprotein A-I	S	Familial
AApoA-II	Apolipoprotein A-II	S	Familial
AGel	Gelsolin	S	Familial
ALys	Lysozyme	S	Familial
AFib	Fibrinogen α -chain	S	Familial
ACys	Cystatin C	S	Familial
ABri	ABriPP	L	Familial dementia
ADan	ADanPP	L	Familial dementia
A β	A β protein precursor (A β PP)	L	Alzheimer's disease, aging
APrP	Prion protein	L	Spongiform encephalopathies
ACal	(Pro)calcitonin	L	C-cell thyroid tumors
AIAPP	Islet amyloid polypeptide	L	Islets of Langerhans
			Insulinomas
AANF	Atrial natriuretic factor	L	Cardiac atria
APro	Prolactin	L	Aging pituitary
			Prolactinomas
AIns	Insulin	L	Iatrogenic
AMed	Lactadherin	L	Senile aortic, media
AKer	Kerato-epithelin	L	Cornea; familial
A(tbn)	to be named	L	Pindborg tumors
ALac	Lactoferrin	L	Cornea; familial

Systemic Amyloidosis

- Fibril protein and related diseases
 - A amyloidosis protein (AA)
 - Formed by N-terminal proteolytic fragments of the acute-phase reactant serum amyloid A (SAA), a polymorphic apolipoprotein of high density lipoproteins (HDL)
 - SAA is an acute-phase protein that increases secondary to chronic inflammatory stimuli (i.e., inflammatory arthritis, leprosy, osteomyelitis, tuberculosis, familial Mediterranean fever, Hodgkin disease, renal cell carcinoma)
- Clinical findings
 - *Cutaneous*: no skin findings
 - *Renal*: proteinuria, nephrotic syndrome and progressive development of renal insufficiency
 - *Gastrointestinal*: constipation, diarrhea and malabsorption
- Treatment: colchicine (to prevent AA amyloidosis in familial Mediterranean fever), treat primary inflammatory condition

AMYLOID LIGHT CHAIN (AL)

- Primary systemic
- Formed by the N-terminal fragment of a monoclonal immunoglobulin light chain, comprising the variable region and a portion of the constant region, produced by a bone marrow plasma cell clone
- Clinical findings
 - Almost any organ can be involved; multiple organ dysfunction is common
 - *Renal*: nephrotic syndrome with peripheral edema
 - *Cardiac*: restrictive cardiomyopathy, arrhythmias
 - *Neurological*: neuropathies, carpal tunnel (17%)
 - *Mucocutaneous*: petechiae, soft tissues enlargement, papules, plaques, macroglossia, ecchymoses, pinch purpura (post-traumatic hemorrhage around orbits, umbilicus, axillae, perianal) (Fig. 23-4)
 - *Hepatic*: hepatosplenomegaly
 - *Gastrointestinal*: bleeding, weight loss

HEREDITARY AMYLOIDOSIS

- Autosomal dominant
- Heterogenous group of diseases associated with mutations in apolipoproteins A1 and A2, fibrinogen A α chain, gelsolin, lysozyme, cystatin C
- Clinical findings depend on the variant protein: deposits primarily in the peripheral nerves, heart, gastrointestinal tract, and vitreous of eyes
- Transthyretin (TTR); familial amyloid polyneuropathy



FIGURE 23-4 Amyloidosis of the eyelid. (Reproduced with permission from Wolff et al: *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- Transport protein synthesized in the liver and choroid plexus, transports thyroxine and retinol
- Clinical findings: peripheral neuropathy, xerosis, seborrheic dermatitis, trauma or burn lesions, neuropathic ulcers, onychomycosis

DIALYSIS-RELATED AMYLOIDOSIS (DRA)

- β -2 Microglobulin (Ab2m) protein accumulates in the serum
- Clinical findings: carpal tunnel syndrome, arthropathies, spondyloarthropathies, bone cysts, visceral amyloid deposition (heart, gastrointestinal tract: macroglossia, bowel infarction and perforation; lungs)

Localized Cutaneous AL Amyloid

- Local production of fibril precursors derived from N-terminal cleavage fragments of monoclonal immunoglobulin light chains
- Localized to skin
- Deposition of AL protein
- One or several nodules on legs/face (Fig. 23-5)
- Histology: atrophic epidermis, masses of amyloid dermis, subcutaneous fat, appears as "cracks in mud," lymphocyttoplasmic infiltrate, Russell bodies: round hyaline, eosinophilic bodies inside/outside of plasma cells (with Ig), foreign-body giant cells
- Treatment: surgical excision, CO₂ laser
- Course: may develop systemic amyloidosis



FIGURE 23-5 Nodular amyloidosis. (Reproduced with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003.)

MACULAR AND LICHEN AMYLOIDOSIS

- Due to altered keratin; amyloid deposits bind to anti-keratin antibodies
- Usually idiopathic or friction related; also associated with connective tissue diseases (i.e., systemic lupus erythematosus)

Macular Amyloidosis

- Affects the upper back and limbs
- May result from constant scratching
- Clinical findings: pruritic brown-gray, reticulated, rippled, macules/patches mainly on upper back, notalgia paresthetica, some postinflammatory hyperpigmentation
- Diagnosis: *direct immunofluorescence*: IgM, C3, Ig, light chains
 - *Histology*: amyloid deposits in papillary dermis, globular, colloid deposition in dermis; do not involve blood vessels or adnexal structures
- *Lichen amyloidosis*
- Clinical findings: closely set, discrete brown-red papules, pruritic; commonly on the legs
- Diagnosis: histology similar to macular amyloidosis but with irregular acanthosis
- Treatment: topical steroids, intralesional steroids, Dimethyl sulfoxide (DMSO), calcineurin inhibitors, PUVA, dermabrasion, acitretin

SENILE AMYLOIDOSIS

- Associated with Alzheimer disease

- Senile/neuritic plaques: neurofibrillary tangles, vascular lesions
- Due to β amyloid = major fibril protein
- Amyloid precursor protein (APP)
- No skin lesions

XANTHOMAS

- Accumulations of lipid-laden macrophages; arise due to lipoprotein disorders
- Lipoproteins: lipids transported in plasma as complexes with specific apoproteins
- Lipoproteins: may be classified according to their buoyant density:
 - *Chylomicrons*: triglycerides (TG) that are incorporated into lipoproteins
 - *Very low density lipoproteins* (VLDLs): hepatic derived triglyceride-rich lipoproteins (contain less TG and more cholesterol compared to chylomicrons)
 - *Intermediate-density lipoproteins* (IDLs)
 - *Low-density lipoproteins* (LDLs): mainly contain cholesterol
 - *High-density lipoproteins* (HDLs): take up free cholesterol from peripheral tissue

Phenotypic Classification of Hyperlipidemias (Table 23-3)

- Familial chylomicronemia syndrome (Frederickson type I hyperlipidemia)
 - *Familial lipoprotein lipase deficiency*: results in chylomicrons containing triglycerides that accumulate in the serum
 - Clinical findings
 - *Cutaneous*: eruptive xanthomas located over the buttocks, shoulders and extensor surfaces
 - Also associated with pancreatitis and lipemia retinalis
 - Laboratory: elevated triglycerides
 - Treatment: diet modification
- Apolipoprotein-C2 deficiency
 - Apo-C2 carried on triglyceride-rich lipoproteins and activates LPL (without LPL, chylomicrons are not degraded)
 - Clinical findings: eruptive xanthomata
 - Treatment: diet modification
- Hypercholesterolemia (Frederickson type II hyperlipidemia)
 - Familial homozygous hypercholesterolemia
 - Genetic deficiency of LDL receptors (remove LDL from the circulation)
 - Clinical findings:
 - Cutaneous: tendinous, tuberous, subperiosteal xanthomas, and xanthomatous plaques, as well as xanthelasmas

TABLE 23-3 Frederickson Classification of Xanthoma

Frederickson Classification (Type)	Condition	Type of Xanthoma
I	Familial chylomicronemia	Eruptive xanthoma
IIa	Familial hypercholesterolemia	Tendon, tuberous, plane (xanthelasma and intertriginous)
	Heterozygous	15% with xanthoma by second decade
	Homozygous	Xanthomata by age 6 years
IIb	Familial combined hypercholesterolemia	Palmar, tuberous, tuberoeruptive, xanthelasma
III	Familial dysbetalipoproteinemia	Palmar, tuberous, tuberoeruptive xanthoma, xanthelasma
IV	Familial hypertriglyceridemia	Rare eruptive xanthomas
V	Mixed Hyperlipidemia	Eruptive xanthomas

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- Laboratory: increased LDL and VLDL levels
 - Treatment: high doses of statins, liver transplantation
 - Familial heterozygous hypercholesterolemia
 - Single abnormal allele for the LDL receptor
 - Clinical findings
 - Cutaneous: tendon xanthomata
 - Laboratory: elevated LDL-cholesterol levels
 - Treatment: statins
 - Defective metabolism of lipoprotein remnants: Dysbetalipoproteinemia (Frederickson type III hyperlipidemia)
 - Accumulation of remnant lipoproteins (chylomicron remnants and VLDL remnants) due to an abnormal isoform of apo-E, named apo-E2 (normal apo-E isoforms promote hepatic remnant uptake)
 - Clinical findings
 - Cutaneous: tuberous xanthomata, planar xanthomas, affecting the palms (xanthoma striatum palmare)
 - Laboratory studies: cholesterol, triglycerides increased; cholesterol to triglyceride ratio raised in VLDL
 - Treatment: fibric acids, nicotinic acid, statin
 - Multifactorial hyperlipidemias
 - Familial hypertriglyceridemia (Frederickson type IV hyperlipidemia)
 - Liver overproduces VLDL and LDL
 - Xanthomas rare
 - Treatment: low fat diet, fibric acid
 - Familial hypertriglyceridemia: chylomicronemia combined with endogenous hypertriglyceridemia (Frederickson type V hyperlipidemia)
 - Combined elevations in levels of chylomicrons and VLDL
 - Clinical findings
 - Cutaneous: eruptive xanthomas
 - Other: pancreatitis
 - Treatment: low fat diet, fibric acids, weight reduction
- Types of Cutaneous Xanthomas**
- Xanthelasma palpebrarum (Fig. 23-6)
 - Most common of the xanthomas
 - Fifty-five percent of the patients may have hyperlipidemia
 - Clinical: symmetric soft, velvety, yellow, flat, polygonal papules around the eyelids
 - Treatment: trichloroacetic acid, surgical excision, cryotherapy, ablative laser treatment
 - Tuberous xanthomas (Fig. 23-7)



FIGURE 23-6 Xanthelasma palpebrarum. (Courtesy of Dr. Asra Ali.)

- Firm, painless, red-yellow nodules
- Can coalesce to form multilobulated tumors
- Develop in pressure areas, such as the extensor surfaces of the knees, the elbows, and the buttocks
- Tendinous xanthomas
 - Subcutaneous nodules related to the tendons or the ligaments
 - Most common locations are the extensor tendons of the hands, the feet, and the Achilles tendons
 - Often related to trauma
- Eruptive xanthomas
 - Crops of small, red-yellow papules on an erythematous base, pruritus is common
 - Most commonly arise over the buttocks, the shoulders, and the extensor surfaces of the extremities
 - May resolve spontaneously over weeks
- Planar xanthomas
 - Yellow macules, soft papules
 - Palmar crease (xanthoma striatum palmare), eyelids (xanthelasma palpebrarum)
 - Generalized plane xanthomas: cover large areas of the face, neck, thorax, and flexures
 - May be associated with monoclonal gammopathy
- Xanthoma disseminatum
 - Occur in normolipemic patients
 - Red-yellow papules and nodules with a predilection for the flexures
 - Mucosa of the upper part of the aerodigestive tract is involved
 - Usually resolves spontaneously
- Verruciform xanthoma
 - Occurs in normolipemic patients



FIGURE 23-7 Tuberous xanthoma. (Reproduced with permission from Wolff et al: *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- Oral cavity of adults as a single papillomatous yellow lesion
- Reactive condition with benign behavior
- Histology: vacuolated macrophages filled with lipid (foamy macrophages); lipids dissolved and removed from the tissue during histologic processing; multinucleated histiocytes (Touton giant cells)
- Treatment: local excision, topical trichloroacetic acid, electrodesiccation, laser therapy
- Prognosis: recurrences can occur

DIABETES-ASSOCIATED DISEASES

Acanthosis Nigricans

- Marker of insulin resistance
- Excessive amounts of circulating insulin bind with insulin-like growth factor receptors on keratinocytes and dermal fibroblasts; increased proliferation of keratinocytes and fibroblasts
- Activation of tyrosine kinase receptors expressed on basal cells of the epidermis
- Fibroblast growth factor receptor 3 (FGFR3) mutations
- Exert antiapoptotic and mitogenic effects on keratinocytes

- Associated conditions:
 - Obesity: most common type; patients have higher fasting plasma insulin levels compared to control subjects
 - Syndromic
 - Insulin resistance
 - Type A syndrome: reduced number or dysfunction of insulin receptors, related to obesity
 - Hyperandrogenemia, insulin resistance, and acanthosis nigricans (HAIR-AN) syndrome
 - Polycystic ovaries or signs of virilization (hirsutism, clitoromegaly), high risk of developing diabetes
 - Type B syndrome: due to antibodies directed against the insulin receptor: uncontrolled diabetes mellitus, ovarian hyperandrogenism, or an autoimmune disease (SLE)
 - Examples of other associated syndromes and diseases: Cushing syndrome, connective tissue diseases (lupus erythematosus, scleroderma, dermatomyositis), hypothyroidism
 - Genetic benign
 - Autosomal dominant
 - May develop at birth or during childhood; progresses until puberty, then stabilizes or regresses
 - Drug-induced: nicotinic acid, systemic corticosteroids, oral contraceptives
 - Malignant: most commonly adenocarcinoma of gastrointestinal tract
- Clinical findings
 - Symmetric, hyperpigmented, velvety plaques with accentuation of skin markings (Fig. 23-8)
 - Develop in flexures, such as axillae, groin, and posterior neck
 - Acrochordons (skin tags) often are found



FIGURE 23-8 Acanthosis nigricans. (Courtesy of Dr. Asra Ali.)

- Tripe palms
 - Thickening of the palms with accentuation of the ridges and furrows; thought to exist as a form of palmar acanthosis nigricans
 - Associated with acanthosis nigricans (75%)
 - Associated with cancer; pulmonary carcinoma is the most common, followed by lung
- Diagnosis:
 - Laboratory findings: for patients with syndromic AN-glucose tolerance test; total testosterone, dehydroepiandrosterone sulfate (DHEA-S), gonadotropic concentrations, cortisol levels
 - Histology: hyperkeratosis, papillomatosis, and slight irregular acanthosis with minimal or no hyperpigmentation; the dermal papillae project upward as finger-like projections
- Treatment: correct the underlying disease, topical tretinoin, vitamin D3 analogs

Necrobiosis Lipoidica Diabetorum (NLD) (Fig. 23-9)

- Degenerative disease of collagen in the dermis and subcutaneous fat
- Diabetics account for 14–65% of all cases; it occurs in 0.03% of diabetics
- Clinical findings:



FIGURE 23-9 Necrobiosis lipoidica diabetorum. (Reproduced with permission from Wolff et al: *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- Well-circumscribed, symmetric, oval or irregularly shaped indurated plaques with central atrophy, yellow pigmentation, and telangiectatic vessels on pretibial areas, periphery of lesions have red-brown or violaceous pigmentation
- Koebner phenomenon present; decreased pinprick sensation
- Lesions are typically multiple and bilateral and may ulcerate
- Diagnosis
 - Histology: neutrophilic vasculitis; granulomas are arranged in a tierlike fashion and are admixed with areas of collagen degeneration, thickening of the blood vessel walls; immune complex vasculitis
 - Direct immunofluorescence: immunoglobulin M, immunoglobulin A, C3, and fibrinogen in the blood vessels
 - Serum: increased fibronectin, factor VIII-related antigen, α_2 macroglobulin
- Treatment: topical and intralesional steroids, antiplatelet aggregation therapy with aspirin and dipyridamole; niacinamide, excision and grafting
- Prognosis: progression of lesion does not correlate with glycemic level, course is indolent, spontaneous remission in less than 20% of patients

Diabetic Dermopathy

- Most common cutaneous finding in diabetes
- Clinical findings:
 - Round to oval atrophic hyperpigmented lesions on the pretibial areas of the lower extremities; sites of trauma
 - Brownish hyperpigmentation hemosiderin deposits
- Histology: edema of the papillary dermis, thickened superficial blood vessels, extravasation of erythrocytes, mild lymphocytic infiltrate
 - Course: resolves spontaneously

Bullosis Diabeticorum

- Confined to the extremities
- Occurs spontaneously; noninflammatory
- Types
 - Sterile with fluid: heals without scarring; histology shows intraepidermal cleavage without acantholysis
 - Hemorrhagic: heals with scarring, histology shows cleavage below the dermal-epidermal junction, destruction of anchoring fibrils
 - Multiple nonscarring bullae: sun-exposed areas, histology: cleavage at lamina lucida
 - Prognosis: runs a benign course

Diabetic Ulcers

- Ischemic ulcers

- Neuropathic ulcers in patients with diminished sensation, especially on areas of pressure sites; presents with a keratotic rim

Acquired Perforating Dermatoses

- Seen in patients with kidney failure associated with diabetes
- Kyrle disease (acquired perforating dermatosis): papules with a keratotic plug due to elimination of collagen and elastin, seen on the extensor surfaces of the lower extremities; histology shows hyperkeratosis surrounding a plug of degenerated material

GLUCAGONOMA SYNDROME

- Caused by glucagon-secreting tumors of the alpha cells of the pancreas, slow growing
- Associated with: hyperglucagonemia, diabetes mellitus, hypoaminoacidemia, cheilosis, normochromic, normocytic anemia, venous thrombosis, neuropsychiatric features
- Mucocutaneous findings: necrolytic migratory erythema (NME), predilection for the perineum, buttocks, groin, lower abdomen, and lower extremities; annular erythematous patches with blisters that erode, atrophic glossitis, cheilosis, dystrophic nails, and buccal mucosal inflammation
- Prognosis: 50% of tumors are metastatic at the time of diagnosis

Carotenemia

- Associated with ingestion of yellow and green vegetables
- Slow conversion of beta-carotene (provitamin A) to vitamin A
- Accelerated by thyroxine and hyperthyroidism
- Conversion occurs in the mucosal cells of the small intestine
- Clinical findings: carotenoderma: yellow/orange color of skin, greatest concentration is in areas with increased sweating (nasolabial folds, forehead); lipophilic: may take months before color of skin returns to normal, sclera and mucous membranes are spared (unlike in jaundice)
- Diagnosis: carotene excreted in the stool, skin, and urine

THYROID DERMOPATHY

- Associated with Graves disease (0.5–4%)
- Stimulatory autoantibodies directed at the TSH receptor are the cause of hyperthyroidism

- Clinical findings
 - Graves disease is characterized by goiter, increased perspiration, heat intolerance, tachycardia, and exophthalmos
 - Cutaneous: warm and moist skin, with smooth texture; thin scalp hair, nails are thin, soft and friable with possible onycholysis with an upward curvature (plummer's nail); hyperpigmentation of the skin (diffuse or local)
 - Pretibial myxedema (PTM) (Fig. 23-10): due to deposition of hyaluronic acid in the dermis and subcutis; lateral or anterior aspect of the legs with pink to purple-brown bilateral, firm, nonpitting, asymmetric plaques or nodules, peau d'orange texture. IgG antibodies directed at the thyroid stimulating hormone receptor (TSHR-Ab) are present in 80% of patients, elephantiasic form presents with verruciform plaques
- Diagnosis
 - Histology: hyperkeratosis, mucin (glycosaminoglycans) in the reticular dermis, and a Grenz zone of relatively normal papillary dermis; stains blue with Alcian blue, at a pH of 2.5, and colloidal iron stains; metachromasia with toluidine blue stain
 - Laboratory tests: serum thyroid function tests, thyroid-stimulating immunoglobulins
- Treatment: pretibial myxedema: topical or intralesional corticosteroids; plasmapheresis; octreotide



FIGURE 23-10
Thyroid dermatopathy.
Pretibial myxedema.
(Reproduced with
permission from Wolff
et al: *Fitzpatrick's
Dermatology in General
Medicine, 7th Ed.* New
York: McGraw-Hill;
2008.)

OSTEOMA CUTIS

- Presence of bone within the skin in the absence of a preexisting or associated lesion
- Associated with:
 - Fibrodysplasia ossificans progressive: AD; R206H mutation, endochondral, deep bone formation, early mortality
 - Albright hereditary osteodystrophy: GNAS 1 mutations (adenylate cyclase), complex inheritance pseudohypoparathyroidism and pseudopseudohypoparathyroidism, short stature, round face, defective teeth, mental retardation, brachydactyly (short fourth metacarpals and metatarsals), tetany in patients with hypocalcemia, osteomas of the soft tissue and skin (intramembranous), milium cysts of the face, following acne, neurotic excoriation; milium-like ossification of syringomas in Down syndrome, progressive osseous heteroplasia, intramembranous ossification, asymptomatic papules/nodules; "rice-grain" texture
- Plate-like osteoma cutis: limited form of POH
- Secondary types: cutaneous ossification can also occur by metaplastic reaction to inflammatory, traumatic, and neoplastic processes
- Diagnosis
 - Laboratory findings: serum calcium and parathyroid hormone (PTH) for hypoparathyroidism and pseudohypoparathyroidism (Albright's)
 - Excisional biopsy
- Treatment: excision or laser resurfacing; tretinoin for milium cysts

NEPHROGENIC SYSTEMIC FIBROSIS

- Idiopathic acquired fibrosing disorder
- Pathogenesis is unknown, most likely multifactorial. Most common factor is the presence of acute or chronic renal insufficiency. Also seen in renal insufficiency patients receiving gadolinium dye for MR-angiography
- Clinical findings
 - Symmetric, indurated plaques with brawny hyperpigmentation; may also present with distinct papules and subcutaneous nodules, extremities more commonly affected than trunk; face usually spared, joint contractures with pain may be present; yellow plaques in sclera; fibrosis of heart, lungs, and skeletal muscle
- Diagnosis
 - Histology: thickened collagen bundles with surrounding clefts, mucin deposition, proliferation of fibroblasts and elastic fibers

- Occasional CD34-positive and procollagen I positive dendritic fibroblasts (“circulating fibrocyte”)
- Gadolinium found on tissue spectroscopy
- Prognosis: course is progressive
- Treatment: there is no single treatment that has been shown to be effective

POLYCYSTIC OVARIAN SYNDROME

- Occurs in the presence of androgen excess with chronic anovulation without specific underlying disease of the adrenal or pituitary glands
- Other causes: congenital adrenal hyperplasia (CAH), ovarian and adrenal tumors, drugs (anabolic steroids, progestens, danazol)
- Diagnostic criteria requires the presence of two of the following three criteria:
 - Oligoovulation (fewer than eight menses per 12-month period) and/or anovulation
 - Clinical hyperandrogenism and/or biochemical signs of hyperandrogenism (hyperandrogenemia)
 - Polycystic ovaries (≥ 12 follicles in each ovary measuring 2–9 mm in diameter and/or increased ovarian volume [> 10 mL]) by ultrasonography
- Cutaneous findings: acne vulgaris, seborrhea, androgenic alopecia, hirsutism, acanthosis nigricans; patients with virilization (secondary to severe hyperandrogenism): clitoromegaly, deepening of voice, increased muscle mass
- Other: secondary amenorrhea, infertility, menstrual alterations, obesity, insulin resistance with metabolic syndrome, risk of atherosclerosis
- Diagnosis
 - Laboratory: serum total testosterone, dehydroepiandrosterone-sulfate (DHEA-S) and prolactin; if total testosterone is greater than 200 ng/dL an ovarian tumor is suspected; if DHEA-S is more than 2–3 times the upper limit of normal adrenal tumor is suspected; 17-hydroxyprogesterone to evaluate for late-onset CAH, deficient follicle stimulating hormone (FSH), increased luteinizing hormone (LH), evaluation of glucose intolerance
 - *Imaging*: transvaginal ultrasound for evaluation of ovarian tumor, CT scan of adrenal glands to exclude and adrenal mass
- Treatment: oral contraceptives, antiandrogens (i.e., spironolactone), metformin, oral contraceptive pills

HYPOPARATHYROIDISM/ PSEUDOHYPOPARATHYROIDISM

- Hypoparathyroidism can result from surgery, infiltrative disorders, autoimmune conditions, or may be idiopathic
- Pseudohypoparathyroidism is a heritable disorder of target organ unresponsiveness to parathyroid hormone
- Cutaneous findings: xerosis, hyperkeratosis, brittle nails, transverse ridging, coarse and sparse hair, eczematous dermatitis, Albright hereditary osteodystrophy (short neck, brachydactyly, subcutaneous ossifications)

CUSHING SYNDROME

- Results from chronic glucocorticoid excess, caused mainly by pituitary hypersecretion of adrenocorticotrophic hormone (ACTH) or by non-pituitary tumors, adrenal hypersecretion of hyperinsulinism or exogenous administration of corticosteroids
- Clinical findings: progressive central (centripetal) obesity, fat deposition in the cheeks resulting in moon facies
 - *Cutaneous*: atrophic skin, loss of subcutaneous tissue, easy bruising, striae densae (violaceous, > 1 cm) commonly seen on upper arms, shoulders, axillae, breasts, hips, buttocks and upper thighs; hyperpigmentation may be generalized, most evident in areas exposed to light; vellus hair on forehead and cheeks; if androgen excess is present then hirsutism, oily facial skin, and acneiform rashes may occur
- Diagnosis: 24-hour urinary free cortisol (UFC), serum ACTH to define the source (low: adrenal, normal to high: pituitary; very high: ectopic)
- Treatment: dependent on the cause. Surgery for pituitary, adrenal, or ectopic tumors with possible radiation or chemotherapy; medications that inhibit steroid synthesis

ADDISON DISEASE

- Most common cause of chronic primary adrenal insufficiency due to autoimmune adrenalitis
- Other etiologies: infection, hemorrhage, neoplasia
- Clinical findings
 - Cutaneous: generalized hyperpigmentation due to increased melanin content in the skin, due to the melanocyte-stimulating activity of high plasma

- ACTH concentration; nails with longitudinal pigmented bands
- Diagnosis: cosyntropin (synthetic ACTH) stimulation test with serum cortisol measurements; plasma ACTH, hyponatremia, hyperkalemia, hyperchloremic metabolic acidosis; CT of adrenal glands
 - Treatment: replace glucocorticoids

ACROMEGALY

- Due to excessive secretion of growth hormone (GH)
- Usually due to a pituitary adenoma
- Clinical findings
 - Cutaneous: soft tissue overgrowth, enlarged jaw (macrognathia), swollen hands and feet, thickened skin with a doughy feel, coarse facial features with accentuation of facial folds; thick eyelids, enlarged lips, thick and hard nails, hyperhidrosis (50%)
- Diagnosis: serum insulin-like growth factor (IGF-1), GH dependent; serum GH after a glucose load; magnetic resonance imaging (MRI) of pituitary gland
- Treatment: surgical resection of the pituitary tumor, somatostatin analogues (if surgery not curative)

QUIZ

Questions

1. A 65-year-old Caucasian woman presents with yellow plaques over both shins with telangiectasia and decreased sensation. She also reports recent worsening of her vision and ulcers on the plantar surface of her feet. Histologic evaluation of a shin plaque is most likely to show:
 - A. "Red snappers" on fite stain
 - B. Perivascular lymphocytes with "tight cuffing"
 - C. Granulomatous dermatitis
 - D. Lipid-laden macrophages
 - E. Cholesterol clefts
2. Which of the following disorders is most related to abnormalities in endochondral ossification?
 - A. Albright's hereditary osteodystrophy
 - B. Progressive osseous heteroplasia
 - C. Plate-like osteoma cutis
 - D. Fibrodysplasia ossificans progressiva
 - E. Miliary facial osteomas
3. The perforating dermatosis most related to diabetic neuropathy is:
 - A. Kyrles disease
 - B. Elastosis perforans serpiginosa
 - C. Reactive perforating collagenosis
 - D. Perforating granuloma annulare
 - E. Perforating folliculitis
4. The rate-limiting enzyme in heme biosynthesis is:
 - A. Porphobilinogen deaminase
 - B. Ferrochelatase
 - C. ALA synthase
 - D. Uroporphyrinogen decarboxylase
 - E. Protoporphyrinogen oxidase
5. A 30-year-old Caucasian man presents with scarring and blisters over his dorsal hands, tachycardia, and occasional constipation. What test would be most useful in confirming a diagnosis of variegate porphyria?
 - A. Normal urine
 - B. Plasma fluorescence at 626 nm
 - C. Uroporphyrinogen/coproporphyrinogen ratio 8:1
 - D. Fecal coproporphyrin > protoporphyrin
 - E. Urine fluorescence at 626 nm
6. Which of the following diseases is LEAST likely to be diagnosed via 24-hour urine porphyrin collection?
 - A. Porphyria cutanea tarda
 - B. Erythropoietic protoporphyria
 - C. Erythropoietic porphyria
 - D. Hereditary coproporphyria
 - E. Hepatoerythropoietic porphyria
7. A 30-year-old man presents with recent onset of arthralgias, darkening pigmentation on his face, and darkening of his urine. He most likely has a defect in which enzyme?
 - A. Cystathione β synthetase
 - B. Tyrosinase
 - C. Homogentisic acid oxidase
 - D. Ferrochelatase
 - E. α -galactosidase
8. A 45-year-old man with hepatitis C and severe anemia develops blisters over the dorsum of his hands and significant elevation of his urine uroporphyrinogen. The BEST treatment for this patient would be:
 - A. Phlebotomy twice weekly
 - B. Hydroxychloroquine orally twice daily
 - C. Hydroxychloroquine orally twice weekly
 - D. Stem cell transplant
 - E. Topical metronidazole

9. Development of herpetiform corneal ulcers, palmoplantar keratoderma, and painful acral lesions is most closely related to the metabolism of which amino acid?
 - A. Tyrosine
 - B. Glycine
 - C. Arginine
 - D. Histidine
 - E. Leucine
10. Which of the following is most likely to involve deposition of a keratin derived substance on the legs?
 - A. Nodular amyloid
 - B. Macular amyloid
 - C. Lichen amyloid
 - D. Familial mediterranean fever
 - E. Beta-2-microglobulin derived amyloid

Answers

1. C. Necrobiosis lipoidica diabetorum may be seen in 0.3% of diabetics, most commonly type 1. Clinical presentation generally consists of yellow atrophic plaques on both lower extremities. Pathology classically demonstrates a granulomatous dermatitis with “layered” appearance.
2. D. Fibrodysplasia ossificans progressiva is a genetic disorder resulting in deep, endochondral bony deposits with early mortality.
3. A. Kyrle disease (acquired perforating dermatosis) is most commonly found on the legs of diabetic patients requiring dialysis.
4. C. The condensation of glycine and succinyl CoA by ALA synthase in the mitochondria is the rate limiting step.
5. B. Variegate porphyria and PCT may have similar cutaneous findings, with variegate porphyria more likely to have acute abdominal findings. VP patients have a characteristic plasma fluorescence at 626 nm and fecal proto > copro. PCT would have a uro/copro ratio of 8:1.
6. B. EPP, a deficiency in ferrochelatase, has characteristically normal urine on exam. Stool and blood protoporphyrin levels will be abnormal.
7. C. Alkaptonuria, a defect in homogentisic acid oxidase, may present in childhood or adulthood. Children classically present with black urine (if pH > 7); adults tend to have more joint disease and skin darkening. Treatment is supplemental vitamin C.
8. C. PCT is best treated with serial phlebotomy. In a patient with severe anemia, however, phlebotomy is contraindicated. Second-line treatment may include low dose antimalarials.
9. A. Richner-Hanhart syndrome is an example of a tyrosinemia with a defect in hepatic tyrosine aminotransferase. Treatment is with a low phenylalanine and tyrosine diet.
10. C. Lichen amyloidosis is a deposition of keratin-derived amyloid most commonly found on the legs. Macular amyloid, while also keratin-derived, is most commonly found on the upper back. Familial Mediterranean fever is related to AA protein. Beta-2-microglobulin amyloid is a hemodialysis associated protein that accumulates in end organs.

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DERMATOLOGIC MEDICATIONS

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BASIC PHARMACOLOGIC PRINCIPLES

- Pharmacokinetics: includes the extent and rate of absorption, distribution, metabolism and excretion (ADME) of medications in the body.
- Pharmacodynamics: defined as the effects of medications on the body (biochemical and physiological)

Concepts of Adverse Effects

- *Toxicity*: excessive doses or drug levels leading to undesired effects
- *Pharmacologic effect*: normal drug levels resulting in positive or negative effects
- *Adverse effect (side effect)*: harmful and undesired effect resulting from a medication
- *Idiosyncratic reaction (type B reaction)*: drug reaction which occurs rarely and unpredictably

SYSTEMIC MEDICATIONS

Glucocorticosteroids

- Pharmacology
 - Cortisol binding globulin (CBG, transcortin) binds 90–95% of plasma cortisol; the free fraction is the active form; CBG is increased by pregnancy, estrogen treatment, and hyperthyroidism
- *Short acting*: cortisone and hydrocortisone; mineralcorticoid potency > glucocorticoid potency, with cortisone having the lowest glucocorticoid potency
- *Intermediate acting*: prednisone, prednisolone, methylprednisolone, and triamcinolone; glucocorticoid potency > mineralcorticoid potency

- *Long acting*: dexamethasone and betamethasone; glucocorticoid potency only no mineralcorticoid potency
- Mechanism of action
 - Binds to cytosolic receptor, translocates to nucleus, and then binds to glucocorticoid response elements (GRE) on DNA
 - Corticosteroids (CS) reduce the effects of transcription factors that increase the inflammatory response: AP-1 (composed of Jun, Fos or activating transcription factor) and NF- κ B (nuclear factor- κ B)
 - Decreased synthesis of proinflammatory molecules: cytokines, interleukins, adhesion molecules, growth factors, and proteases
 - CS induced apoptosis in lymphocytes and eosinophils
- *Metabolic effects*: increased blood glucose secondary to gluconeogenesis
- *Glucocorticoid effects*: increased appetite
- *Mineralocorticoid effects*: increased sodium retention due to vasoconstriction; results in hypertension and congestive heart failure in susceptible patients; hypokalemia, increased lipids, Cushingoid change, protein catabolism (except in liver), leading to negative nitrogen balance, increase plasma fatty acids and ketone body formation via increased lipolysis and decreased glucose uptake into fat cells, decrease plasma adrenocorticotropic hormone (ACTH), decrease fibroblasts production of collagen
- *Gastrointestinal effects*: increased gastric acid and pepsin secretion, peptic ulcer disease, fatty liver changes, esophageal reflux, nausea and vomiting
- *Skeletal effects*: osteoporosis, osteonecrosis
- *Ocular effects*: posterior subcapsular cataracts

- *Pulmonary effects*: increase surfactant production in fetal lungs
- *Psychiatric effects*: euphoria, psychoses
- *Cutaneous effects*: telogen effluvium, hirsutism, fat atrophy, acne, increased infection risk, poor wound healing
- *Other effects*: myopathy, pancreatitis, adrenal suppression
- Adverse effects may be reduced by alternate day dosing except for risk of osteoporosis, osteonecrosis, and cataracts
- Interval between doses decreases chance of hypothalamic, pituitary, adrenal (HPA) axis suppression compared to actual dose of steroids
- Pregnancy category C

Sulfones and Sulfonamides

- The enzyme dihydropteroate synthase is the target of sulfonamide drugs, which are used extensively in the control of many infections
- Sulfonamides (antimicrobial agents) and sulfones (anti-inflammatory agents) differ in chemical structures and uses

DAPSONE

- Sulfone derivative
 - Mechanism of action
 - Inhibits neutrophil myeloperoxidase and impairs neutrophil chemotaxis, by inhibiting neutrophil adhesion to vascular endothelium integrins
 - Competitive antagonist of dihydropteroate synthetases (causes reduction of folic acid)
 - Metabolism: acetylation (by N-acetyltransferase) and hydroxylation occur in the liver
 - Adverse effects
 - N-hydroxylation of dapsone occurs by P-450 in the liver. The metabolic products are responsible for the hematologic effects of dapsone: methemoglobinemia and hemolytic anemia
 - Dapsone hypersensitivity/mononucleosis-like syndrome: hepatitis, photosensitivity, agranulocytosis (first 3–12 weeks); lupus erythematosus, hypoalbuminemia, fever, hypothyroidism
 - Hemolytic anemia and hemolysis: glucose-6 phosphate dehydrogenase (G6PD) deficient patients are more susceptible
 - Methemoglobinemia: dose-related hemolysis in patients with methemoglobin reductase deficiency; treat with methylene blue (not effective in G6PD deficient patients) or cimetidine
 - Idiosyncratic effects:
 - *Hematologic*: leukopenia, agranulocytosis (occurs within first 12 weeks)

- *Hepatic*: hepatitis, cholestatic jaundice, hypoalbuminemia
- *Neurologic*: peripheral neuropathy (predominantly motor; however, sensory defects can occur), usually reversible; psychosis
- *Cutaneous*: toxic epidermal necrolysis, morbiliform rash, exfoliative erythroderma
- *Gastrointestinal*: gastric irritation, anorexia
- Laboratory studies
 - *Initial baseline*:
 - ▲ Complete blood counts, liver function tests, renal function tests, urinalysis, glucose-6 phosphate dehydrogenase (G6PD) level
 - *Monitor*:
 - ▲ Complete blood counts (CBCs), recommended weekly to biweekly for first month of therapy and monthly to bimonthly thereafter for the next 5 months
 - ▲ Liver function tests every 3 months
- Interactions with other medications
 - May inhibit anti-inflammatory effects of clofazimine
 - Probenecid and folic acid antagonists increase dapsone toxicity
 - Trimethoprim/sulfamethoxazole taken with dapsone may increase toxicity of both drugs
 - Rifampin, para-amino benzoic acid and activated charcoal may decrease absorption.
- Contraindications: documented hypersensitivity; known G6PD deficiency or methemoglobin reductase deficiency
- Pregnancy category C

SULFASALAZINE

- Mechanism of action: unknown; inhibits neutrophil chemotaxis
- Adverse effects: gastrointestinal upset, fatigue, headache, drug eruption and photosensitivity; slow acetylators are prone to toxicity, agranulocytosis (within first three months of therapy)
- Pregnancy category B

Aminoquinolones

HYDROXYCHLOROQUINE/CHLOROQUINE/QUINACRINE

- Mechanism of action
 - Inhibits chemotaxis of eosinophils and neutrophils, impairs antigen-antibody complex formation, inhibits release of interleukin 2 (IL-2) from CD4+ T cells, decreases lysosomal size
- Adverse effects
 - Crosses placenta and may cause ocular, CNS, or ototoxicity in fetus; do not use in breast-feeding mothers
 - *Ocular toxicity*: reversible premacularopathy and irreversible true retinopathy; only

hydroxychloroquine and chloroquine are associated; risk is greatest with chloroquine, corneal deposition (results in halos), blurred vision, photophobia

- *Hemolytic anemia* in patients with G6PD deficiency
- *Mucocutaneous effects*: blue/gray mucocutaneous pigmentation and transverse bands in nailbeds due to hemosiderin and melanin; quinacrine may cause yellow pigmentation; progressive bleaching of hair roots with chloroquine
- *Worsening of psoriasis*, mainly chloroquine
- *Gastrointestinal*: nausea and vomiting
- *Neuromuscular*: headache, psychosis, muscular weakness
- Eye studies
 - Slit lamp and fundoscopic eye exam, visual field test
- Laboratory tests:
 - CBC, G6PD, chemistry panel
 - Monitor: eye exam every 6 months, labs (as above) every three months, then every four to six months.
- Interactions with other medications:
 - Cimetidine may increase serum levels of chloroquine
 - Digoxin levels may be elevated
 - Magnesium trisilicate may decrease absorption of 4-aminoquinolones
- Antimalarial contraindications:
 - *Absolute*: hypersensitivity to the medication
 - *Relative*: pregnancy, lactation, severe blood dyscrasia, significant hepatic dysfunction, significant neurologic disorder, retinal or visual field changes, psoriasis
- Pregnancy category C

Antimetabolic and Cytotoxic Agents

- Antimetabolites: mimic natural molecules and are most active while DNA is being synthesized in the S phase
 - Require a target-cell population that is proliferating in order to exert their effect
 - Side effects are most prominent in cells with an innately high proliferative index (e.g., bone marrow)
- Alkylating agents interact with preformed DNA molecules
 - Affect proliferating populations of cells and cells that are not actively synthesizing DNA
 - Have a greater propensity for mutagenicity

METHOTREXATE

- Mechanism of action
 - S phase antimetabolite; competitively and irreversibly inhibits dihydrofolate reductase to

block folate metabolism; partially reversibly inhibits thymidylate synthetase downstream to block DNA synthesis

- Adverse effects: gastrointestinal distress, renal failure, liver cirrhosis/hepatotoxicity (low risk if cumulative dose is below 1.5 g), abortifacient, pancytopenia (first 4–6 weeks), acute pneumonitis, pulmonary fibrosis, nephrotoxicity, phototoxicity, acral erythema, radiation recall, lymphoma, ulcerative stomatitis
- Folic acid supplementation can decrease gastrointestinal side effects
- Liver biopsy after cumulative dose of 1.5 g to diagnose methotrexate induced hepatic fibrosis.
- Drug interactions
 - Increased methotrexate levels and increased toxicity: salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), probenecid, sulfonamides, dipyridamole, cholramphenicol, phenothiazine, phenytoin, tetracycline
- Laboratory studies
 - Monitor: liver function tests, CBC, lipid panel, test for pregnancy, periodic liver biopsy (most suggest after 1.5 g cumulative dose), renal function test, serologic test for hepatitis
 - Leucovorin (folinic acid) given for acute toxicity
 - Pregnancy category X; recommended that men are off of methotrexate 3 months and women are off of methotrexate one ovulatory cycle before trying to conceive

AZATHIOPRINE

- Mechanism of action
 - 6 thioguanine (active metabolite of azathioprine), a purine analog, inhibits DNA/RNA synthesis and repair; it is immunosuppressive.
 - Three enzymes involved in metabolism after azathioprine is absorbed and converted to 6 Mercaptopurine (6MP):
 - *Hypoxanthine-guanine phosphoribosyl transferase* (HGPRT): results in 6-thioguanine (active form of 6 MP)
 - *Xanthine oxidase* (XO): 6 MP catabolized into inactive metabolites
 - *Thiopurine methyl transferase* (TPMT): 6 MP catabolized to inactive metabolites
- Adverse effects
 - Malignancy: lymphoproliferative, squamous cell carcinoma of skin
 - Gastrointestinal distress
 - Hypersensitivity syndrome
 - Myelosuppression/pancytopenia: increased risk in patients with thiopurine methyltransferase deficiency
- Other effects: hepatitis, pancreatitis, teratogenicity

- Patients with Lesch-Nyhan syndrome lack HGPRT and are resistant to the cytotoxic effects of the drug
- Drug interactions
 - Allopurinol inhibits xanthine oxidase causing increased toxicity
 - ACE inhibitors and folate antagonists can increase myelosuppression
 - Warfarin levels may decrease
- Laboratory studies:
 - LFTs, CBC, pregnancy, baseline TPMT
- Pregnancy category D

MYCOPHENOLATE MOFETIL (MMF) AND MYCOPHENOLIC ACID (MPA)

- Mechanism of action
 - MMF is hydrolyzed to MPA (active metabolite) after absorption
 - MPS is an antimetabolite that noncompetitively inhibits inosine monophosphate dehydrogenase (IMPDH) and suppresses de novo purine synthesis: conversion of inosine-5-phosphate and xanthine-5-phosphate to guanosine-5-phosphate
 - MMF is cytotoxic for cells that rely predominantly on de novo purine biosynthesis, such as lymphocytes (T and B), and lack the purine salvage pathway
- Adverse effects: gastrointestinal effects (dose-dependent and most common), anal tenderness, dysuria/urinary frequency, leukopenia, lymphoma, increased risk for infection, increased toxicity in patients with renal impairment, caution in active peptic ulcer disease
- Drug interactions
 - MMF can decrease levels of levonorgestrel containing hormonal contraceptives
 - MMF can increase levels of phenytoin, acyclovir, ganciclovir, and theophylline
 - Hydrocodone, oxycodone, tramadol, NSAIDs may increase risk of seizures
 - Do not administer with antacids due to decreased absorption of MMF
 - Cyclosporine can decrease MPA levels
 - Cholestyramine can decrease MMF levels
- Pregnancy category D

HYDROXYUREA

- Mechanism of action
 - S phase specific; inhibits ribonucleotide reductase, rate limiting step in DNA synthesis
- Adverse effects
 - *Hematologic*: megaloblastosis (all patients), anemia, pancytopenia
 - *Renal*: elevated BUN and creatinine
 - *Hepatic*: elevated transaminases, transient hepatitis

- *Cutaneous*: leg ulcers, dermatomyositis-like eruption on dorsae of hands, diffuse hyperpigmentation, vasculitis, urticaria, fixed drug eruption, photosensitivity, atrophy of skin and nails
- *Other*: flu-like symptoms, radiation recall
- Laboratory studies
 - CBC, urinalysis (UA), liver function tests (LFTs), serum chemistry
- Interactions
 - Avoid other myelosuppressive agents because of the potential for additive bone marrow toxicity
- Pregnancy category D

CYCLOPHOSPHAMIDE

- Mechanism of action
 - Alkylating agent derived from nitrogen mustard, cell-cycle-nonspecific cytotoxic drug; suppresses B cells > T cells (CD8 > CD4), forms DNA cross-linkages
- Adverse effects
 - Carcinogenic: transitional cell bladder carcinoma, AML, non-Hodgkin lymphoma, SCC
 - Hematologic: thrombocytopenia, anemia, leukopenia, bone marrow suppression
 - Gastrointestinal distress, dose-related
 - Genitourinary: hemorrhagic cystitis, azoospermia; acrolein, metabolite of cyclophosphamide, causes bladder toxicity and increased risk of bladder carcinoma; treat with mesna (sodium 2-mercaptoethanesulfonate) binds to acrolein to reduce toxicity
 - Endocrine: amenorrhea
 - Mucocutaneous: acral erythema, anagen effluvium, hyperpigmentation, pigmented band on teeth
 - Pulmonary: pneumonitis/pulmonary fibrosis
- Laboratory studies:
 - chemistry panel, CBC, LFTs, UA
- Pregnancy category D

CHLORAMBUCIL

- Mechanism of action: alkylating agent derived from nitrogen mustard, cell-cycle non-specific, forms DNA cross linkages
- Adverse effects
 - Carcinogenic
 - Hematologic: leukopenia (common, dose-limiting), bone marrow suppression
 - Mucocutaneous: oral ulcers, alopecia
 - Pulmonary: pneumonitis/pulmonary fibrosis
 - Other: azoospermia, amenorrhea, generalized tonic-clonic seizures (especially in children with nephrotic syndrome or adults with seizure history), gastrointestinal effects

- Laboratory studies:
 - CBC, LFTs, chemistry panel, UA
- Pregnancy category D

RETINOIDS

- Hormones that possess vitamin A activity (natural and synthetic forms)
- Small molecule delivers retinol to enzymes to form retinoic acid (active form) or retinyl esters (storage form).
- Forms of vitamin A in mammals: retinol (vitamin A alcohol), retinal (vitamin A aldehyde), retinoic acid (vitamin A acid)
- Cytosolic retinol binding protein (CRABP)
- CRABP found in high levels in the epidermis and in certain diseases: psoriasis, Darier's disease, pytriasis rubra pilaris, keratosis pilaris
- Retinyl esters: hydrolyzed to retinol, irreversibly metabolized to RA and can be converted to retinal.
- Mechanism of action
 - Function in the regulation of cellular proliferation and differentiation and the modulation of immune function and cytokine function
 - Anti-acne effects: retinoids bind to toll-like receptor 2
 - Anti-inflammatory effects include: decreased release of leukotrienes, inhibits immunoglobulin synthesis from B cells, reduction of lymphocyte proliferation and decreased cytotoxic T-lymphocyte induction
 - Anti-tumor effects: inhibition of selected oncogenes and activation of tumor suppressor genes linked to apoptosis
 - Retinoid effects are mediated by two main families of intracellular receptors:
 - *Retinoic acid receptor* (RAR; bound and activated by all-*trans* retinoic acid)
 - *Retinoid X receptor* (RXR; 9-*cis* retinoic acid is the proposed ligand)
- Each family has three receptor subtypes: alpha, beta, and gamma; gamma is the primary receptor subtype in the skin while beta is absent
- Retinoids are transported to the nucleus by cytosolic retinoic acid binding protein (CRABP), binds to RAR or RXR, and acts as a transcription factor for genes containing retinoic acid response elements
- Also acts indirectly by antagonizing other transcription factors such as activating protein 1 (AP1) and nuclear factor-interleukin-6 (NF-IL6) (upregulated in a variety of hyperproliferative and inflammatory conditions)
- Enhances keratinocyte differentiation by increasing filaggrin production, keratohyaline granules, and Odland body secretion of lipids; downregulates keratins 6 and 16
- Inhibits ornithine decarboxylase
- Three generations of synthetic retinoids:
 - *First generation*: (monoaromatic): tretinoin, isotretinoin
 - *Second generation*: (monoaromatic): etretinate and its metabolite, acitretin
 - *Third generation*: polyaromatic, adapalene, bexarotene, tazarotene
- Side effects
 - *Mucocutaneous*: cheilitis, dry skin, pruritus, epistaxis, paronychia, periungual pyogenic granulomas, telogen effluvium
 - *Ophthalmologic*: blepharoconjunctivitis, blurred vision, abnormal night vision
 - *Teratogenicity*: retinoic acid embryopathy, central nervous system abnormalities (hydrocephalus, microcephaly), external ear abnormalities (anotia, small or absent external auditory canals), cardiovascular abnormalities (septal wall and aortic defects), facial dysmorphism, eye abnormalities (microphthalmia), thymus gland abnormalities, and bone abnormalities; monitor BHCG monthly
 - *Skeletal*: long bones, decalcification, progressive calcification of ligaments and tendon insertions, cortical hyperostosis, periosteal thickening, premature epiphyseal closure, and possible osteoporosis
 - *Myalgias and arthralgias*: sometimes associated with high creatinine kinase levels
 - *Neurologic*: headache, fatigue, lethargy, pseudo-tumor cerebri
 - *Psychologic*: anxiety and depression
 - *Lipids*: increase in plasma lipids (dose-dependent), especially triglycerides; increase in cholesterol levels
 - *Gastrointestinal*: elevated LFTs, most commonly the transaminases, can occur in approximately 15% of patients; nausea, diarrhea, abdominal pain

ISOTRETINOIN (13-CIS-RETINOIC ACID)

- Isomer of naturally occurring tretinoin (*trans*-retinoic acid)
- Decreases sebaceous gland size and sebum production; may inhibit sebaceous gland differentiation and abnormal keratinization
- Absorption increased with food intake
- Dose 1–2 mg/kg range
- Isotretinoin has a terminal half-life in plasma of 10 to 20 hours and is completely cleared from the body within 1 month after the drug is stopped
- Pregnancy category X

ACITRETIN/ETRETINATE

- Second-generation retinoids (aromatic retinoids)
- Acitretin: derived from etretinate, has a terminal half-life in plasma of only 2 days

- Following oral absorption, acitretin undergoes extensive metabolism and interconversion by simple isomerization to its 13-*cis* form (*cis*-acitretin)
- Etretinate has a longer half-life than acitretin owing to greater storage of etretinate in adipose tissue; can be formed with concurrent ingestion of acitretin and ethanol
- Oral absorption of acitretin is optimal when given with food
- Acitretin has a terminal half-life of 2 days; however, women who take acitretin must avoid pregnancy for at least 3 years after discontinuing therapy due to conversion to etretinate by alcohol consumption
- Etretinate is stored in body fat deposits; terminal elimination half-life in plasma of about 100 days; detected in serum in trace amounts for as long as 3 years after cessation of therapy
- Pregnancy category X

BEXAROTENE

- Binds to retinoic X receptor, all subtypes; 100-fold stronger than RAR
- Absorption increased by fatty meals
- Monitoring: perform fasting blood lipid determinations before therapy is initiated and weekly until lipid response to the drug is established; obtain and serially monitor baseline CBC, LFTs, and thyroid function tests; advise patients to limit vitamin A supplements and minimize exposure to sunlight and artificial ultraviolet (UV) light
- Bexarotene has a terminal half life of 7 hours; monitor BHCG, LFTs, triglycerides, and TSH monthly (causes central hypothyroidism)
- Pregnancy category X

ANTI-HISTAMINES

- Mast cells express high affinity immunoglobulin E receptor (FCERI) that can be cross linked by an antigen, triggering release of histamine and other mediators
- H1 and H2 subclasses of histamine receptors are expressed in human skin; H1 receptors also found in the brain, smooth muscle cells, endothelial cells, adrenal medulla, and heart
- Inverse agonists at tissue receptor sites
- Binding is reversible
- Affect smooth muscle contraction, stimulation of nitric oxide formation, endothelial cell contraction, and increasing vascular permeability
- Central nervous system effects are due to blockade of central muscarinic receptors
- *First generation H₁ blockers*
- Lipophilic; sedating by crossing blood brain barrier
 - Five classes:
 - *Pipridine*: i.e., cyproheptadine, anti-serotonin effects, pregnancy category B

- *Alkylamine*: i.e., chlorpheniramine, pregnancy category C
- *Ethanolamine*: i.e., diphenhydramine, also inhibits acetylcholine activity and may cause sedation, urinary retention, may exacerbate angle closure glaucoma. Pregnancy category B
- *Piperazine*: i.e., hydroxyzine, may exacerbate porphyria, may cause alterations in T waves on electrocardiography, drowsiness. pregnancy category C
- *Phenothiazine*: i.e., promethazine, pregnancy category C
- *Second generation H₁ blockers*
 - Less lipid soluble, therefore, only small amounts cross the blood-brain barrier; also have longer half-lives, allowing for less frequent dosing and less sedation compared to first generation H1 blockers
 - Cetirizine: carboxylic acid metabolite of hydroxyzine; binds H1 receptors in blood vessels, GI tract, respiratory tract; at high doses it may have anticholinergic effects, pregnancy category B
- Others
 - fexofenadine (pregnancy category C)
 - loratadine (pregnancy category B)
 - desloratidine: drug interactions: Erythromycin and ketoconazole increase desloratidine and 3-hydroxydesloratidine plasma concentrations, but no increase in clinically relevant adverse effects, including no increase in QTc, is observed, pregnancy category C
 - levocetirizine: pregnancy category B
- Drug interactions
 - Increased antihistamine levels: macrolide antibiotics, azole antifungals, HIV-1 protease inhibitors, SSRI antidepressants,
 - Increased toxicity: CNS depressants, MAO inhibitors

Leukotriene Inhibitors

- Leukotriene receptor antagonists or inhibition of leukotriene production
- Zafirlukast, montelukast: bind CysLT1 receptor
- Zileuton: competitive inhibitor of lipoxygenase—inhibits leukotriene formation (LTB1, LTC1, LTD1, LTE1)
- Adverse effects: possible association with Churg-Strauss vasculitis (zileuton), may increase liver enzymes
- Monitor LFTs
- Pregnancy category B, except for zileuton: category C

Antibiotics

BETA-LACTAM ANTIBIOTICS

- Include penicillins and cephalosporins
- Active against many gram-positive, gram-negative, and anaerobic organisms

PENICILLINS

- Mechanism of action
 - Inhibit bacterial cell wall synthesis; leads to activation of autolytic enzymes that kill the bacteria
 - Active against gram-positive organisms and spirochetes
 - Penicillinase-resistant penicillins include dicloxacillin, nafcillin, and oxacillin
 - Beta-lactamase inhibitor; ampicillin-sulbactam, amoxicillin-clavulanic acid: use in the treatment of bite wounds; active against oral anaerobes, streptococci, anaerobes, and staphylococci
- Adverse effects: hemolytic anemia, nephritis, anaphylaxis, TEN (toxic epidermal necrolysis), erythema nodosum, cutis laxa, nail changes
- Ampicillin causes a morbilliform eruption when given to patients with infectious mononucleosis and when co-administered with allopurinol
- Pregnancy category B

CEPHALOSPORINS

- Mechanism of action: inhibit bacterial cell wall synthesis through inhibition of necessary enzymes known as penicillin binding proteins.
- Grouped into four generations according to the spectrum of antibacterial activity:
 - First generation: *Streptococci*, methicillin-sensitive *Staphylococcus aureus*, some gram-negative bacilli
 - Second generation: increased activity against gram-negative bacilli; all are less active against gram-positive bacteria than first-generation drugs
 - Third generation: mostly IV, increased gram negative coverage and less gram positive; gram-negative organisms most often covered by third generation cephalosporins: *Escherichia coli*, *Proteus mirabilis*, *Klebsiella*, indole-positive *Proteus*; also with increased activity (relative to earlier generations) against *Pseudomonas aeruginosa*
 - Fourth generation: comparable to third generation but more resistant to some chromosomal beta-lactamases; penetrates well into CSF; good for *P. aeruginosa*
- Adverse effects: hypersensitivity, diarrhea, nausea, vomiting, abdominal pain, dizziness, Stevens-Johnson syndrome, toxic epidermal necrolysis, *Clostridium difficile* colitis, nail changes, thrombocytopenia, neutropenia, eosinophilia; cross-reactivity with penicillins: immunologic studies: up to 20% and clinical reports: from 5% to 10%
- Drug interactions
 - Probenacid: elevated levels of of B-lactam medications

- Allopurinol: increased hypersensitivity reaction of ampicillin
- Cefaclor: serum sickness-like reaction
- Pregnancy category B

VANCOMYCIN

- Mechanism of action
 - Inhibits bacterial cell wall synthesis and causes secondary damage to the cytoplasmic membrane
 - Active against gram-positive organisms
- Adverse effects: linear IgA bullous dermatosis, bullous eruptions, red-man syndrome, ototoxicity, nephrotoxicity, thrombophlebitis at injection site; erythema, histamine-like flushing, and anaphylactic reactions may occur when administered with anesthetic agents; when taken concurrently with aminoglycosides, risk of nephrotoxicity; neuromuscular blockade may be enhanced when co administered with nondepolarizing muscle relaxants
- Use with caution in patients with renal impairment or with nephrotoxic or ototoxic drugs; facial flushing from histamine release (e.g., red-man syndrome); usually resolves by slowing IV infusion over 2 hours and by giving antihistamines; adjust daily dosing frequency in renal impairment
- Pregnancy category C

TETRACYCLINES: TETRACYCLINE, DOXYCYCLINE, AND MINOCYCLINE

- Mechanism of action
 - Bacteriostatic
 - Binds to 30s subunit of bacterial ribosome, interfering with protein synthesis
 - Active against *Mycoplasma pneumoniae*, *Chlamydia*, *Rickettsia*, *Propionibacterium acnes* and *Vibrio* spp., *Borrelia burgdorferi*, *Mycobacterium marinum*
- Adverse effects: photosensitivity, gastrointestinal disturbances, esophageal ulceration, enamel dysplasia and delayed bone growth in children (younger than 9 years of age), photo-onycholysis, post-acne osteoma cutis, psoriasis exacerbation, vertigo, pseudotumor cerebri, dizziness, vertigo, Fanconi's anemia and uremia in renal disease patients
- Minocycline: autoimmune hepatitis, systemic lupus erythematosus, blue-grey hyperpigmentation, higher incidence of neurologic side effects
- Doxycycline and demeclocycline are the most phototoxic
- Reduce dose in renal impairment; doxycycline is the tetracycline of choice to use in renal failure patients
- Drug interactions: increased levels of warfarin, digoxin, lithium, insulin; increased risk of pseudotumor cerebri with Isotretinoin, decreased absorption of tetracycline due to antacids, other cations

(iron, zinc, bismuth, salts), cimetidine and sodium bicarbonate; possible decreased level of oral contraceptives

- Pregnancy category D

GLYCYCLINES (TIGECYCLINE)

- Mechanism of action
 - Bacteriostatic, structurally similar to tetracyclines
 - Binds to 30S subunit of bacterial ribosome, interfering with protein synthesis; can bypass resistance to tetracyclines, beta lactams, macrolides, and fluoroquinolones
- Adverse effects: similar to tetracyclines; discoloration of teeth, shock, bradycardia, tachycardia
- Pregnancy category D

MACROLIDES: ERYTHROMYCIN, AZITHROMYCIN, CLARITHROMYCIN

- Mechanism of action
 - Bacteriostatic
 - Bind to 50S bacterial ribosomal subunit to inhibit protein synthesis
 - Active against gram-positive organisms (most streptococci and *S. aureus*)
- Adverse effects: gastrointestinal distress, eosinophilia, oral mucosal lesions, xerosis; estolate formulation may cause cholestatic hepatitis (caution in liver disease)
- Drug interactions: certain macrolides inhibit hepatic cytochrome P-450 thus decreasing metabolic clearance of certain drugs including phenytoin, theophylline, warfarin, digoxin, cyclosporine, carbamazepine, benzodiazepines, corticosteroids, omeprazole
 - Digoxin: elevated levels due to gut flora changes
 - Fluconazole: may increase clarithromycin levels
- Pregnancy category B for erythromycin and azithromycin; all others category C

RIFAMPIN

- Mechanism of action
 - Bactericidal
 - Inhibition of DNA-dependent RNA polymerase
- Activity: broad spectrum; staphylococci, *N. meningitis*, *N. gonorrhoeae*, *H. influenza*, poor gram-negative coverage; active against *M. tuberculosis*
- Rapid resistance, therefore, use concomitantly with another agent that covers gram positive organisms
- Drug interactions: decreased effect: oral contraceptives, warfarin, steroids, anti-arrhythmics, phenytoin, phenobarbital, theophylline, β blockers, fluoroquinolones, cyclosporine, acetaminophen, dapsone, oral hypoglycemics
- Adverse effects: orange discoloration of urine, hypersensitivity syndrome: flu-like symptoms, GI

symptoms, CNS symptoms, bullous pemphigoid like lesions, urticaria, mucositis

FLUOROQUINOLONES

- Ciprofloxacin, ofloxacin, gatifloxacin, levofloxacin, moxifloxacin, sparfloxacin, grepafloxacin, norfloxacin, enoxacin
- Mechanism of action
 - Bacteriocidal
 - Inhibits bacterial DNA gyrase (bacterial topoisomerase II)
 - Active against gram-positive organisms (*S. aureus*, streptococci, except ciprofloxacin and ofloxacin) and gram-negative organisms (mycobacteria, *Neisseria gonorrhoeae*)
- Adverse effects: photosensitivity, flushing, hyperhidrosis, affects cartilage formation in children (contraindicated younger than age 18), tendonitis and tendon rupture
- Drug interactions: absorption is decreased when administered with calcium, magnesium, or aluminum containing antacids
- Increased serum levels of theophylline, aminophylline, warfarin.
- Pregnancy category C

LINCOSAMIDES: CLINDAMYCIN, LINCOMYCIN

- Mechanism of action
 - Bacteriostatic
 - Inhibit 50S bacterial ribosomal subunit to inhibit protein synthesis
 - Active against gram-positive organisms (*Staphylococcus aureus*, streptococci) and anaerobes (*Propionibacterium acnes*), aerobic and anaerobic streptococci (except enterococci)
- Adverse effects: photosensitivity, diarrhea, pseudomembranous colitis (owing to overgrowth of *Clostridium difficile*), hepatic dysfunction, morbilliform rash, neuromuscular blockade, erythema multiforme, urticaria, anaphylaxis
- Pregnancy category B

SULFONAMIDES (TRIMETHOPRIM-SULFAMETHOXAZOLE)

- Mechanism of action
 - Interfere with folic acid synthesis by inhibiting synthesis of dihydrofolate reductase (trimethoprim) and dihydropteroate synthetase (sulfonamides)
 - Active against: gram-positive (*S. aureus*) and gram-negative organisms, *Chlamydia*, *Nocardia*, *S. pyogenes*, *S. viridians*, *Enterobacteriaceae*, *H. influenza*
- Adverse effects: TEN, Stevens-Johnson syndrome; high doses may cause bone marrow depression (if signs occur, give 5 to 15 mg/day leucovorin); caution

in folate deficiency hemolysis may occur in individuals with G6PD deficiency

- Drug Interactions: increased warfarin effects, avoid in patients on methotrexate which also affects folic acid metabolism.
- Pregnancy category C; contraindicated in third trimester due to risk of kernicterus

CHLORAMPHENICOL

- Mechanism of action
 - Binds to 50S subunit of bacterial ribosomes and inhibits peptidyl transferase
- Used to treat *Salmonella*, *Haemophilus*, and pneumococcal and meningococcal meningitis in penicillin-sensitive patients; treats verruga peruana
- Adverse effects: gray baby syndrome, gastrointestinal disturbances, anemia
- Pregnancy category C

AMINOGLYCOSIDES

- Mechanism of action
 - Gentamicin, tobramycin, and amikacin
 - Bind to 30S subunit of bacterial ribosomes to inhibit protein synthesis
 - Active against aerobic gram-negative organisms
- Adverse effects: ototoxicity, nephrotoxicity, neuromuscular blockade, injection-site necrosis
- Pregnancy category D

METRONIDAZOLE

- Mechanism of action
 - Forms toxic metabolites in bacteria that inhibit nucleic acid synthesis
 - Active against anaerobes, protozoa
- Adverse effects: glossitis, stomatitis, disulfiram-like reactions with ethanol, mucosal xerosis, vestibular dysfunction
- Pregnancy category B

OXAZOLIDINONES (LINEZOLID)

- Mechanism of action: binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit and prevents the formation of a functional 70S initiation complex
- Adverse effects: thrombocytopenia depending on duration of therapy (generally greater than 2 weeks of treatment), nausea, headache, diarrhea, vomiting, pseudomembranous colitis, tongue discoloration
- Activity: bacteriostatic against enterococci and staphylococci including MRSA, vancomycin-resistant enterococci (VRE), and bactericidal against most strains of streptococci
- Drug interactions: can induce the serotonin syndrome when co-administered with selective serotonin reuptake inhibitors

- Pregnancy category C

Parasiticidal

IVERMECTIN

- Mechanism of action: blocks glutamate-gated chloride ion channels resulting in paralysis of the parasite
- Used to treat onchocerciasis, strongyloidiasis, Norwegian scabies
- Pregnancy category C

THIABENDAZOLE

- Mechanism of action: inhibits helminth specific enzyme fumarate reductase
- Used to treat cutaneous larva migrans
- Adverse events: nausea, vomiting, diarrhea
- Drug interactions: theophylline levels increased
- Pregnancy category C

Antiviral Agents

ACYCLOVIR

- Mechanism of action: inhibits DNA synthesis by inhibiting viral DNA polymerase; initial phosphorylation of acyclovir to acyclovir monophosphate is catalyzed by virus-induced thymidine kinase
- Activity: human herpes viruses, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and to a lesser extent, cytomegalovirus (CMV) (Cytomegalovirus does not produce thymidine kinase, and so the antiviral activity of acyclovir in cytomegalovirus-induced infections is poor)
- Pharmacokinetics: bioavailability of oral acyclovir is low (15% to 30% of an oral dose is absorbed)
- Adverse effects: nephrotoxicity, phlebitis, and encephalopathy with IV infusion, seizures
- Resistant herpes simplex virus (HSV) mutants: *thymidine kinase negative* (*tk-*) or *tk* mutant and hence do not phosphorylate and activate acyclovir; have an altered DNA polymerase that is not as greatly inhibited by the phosphorylated drug
- Pregnancy category B

FAMCICLOVIR

- Mechanism of action
 - Prodrug of the antiviral agent penciclovir; converted to active form via deacetylation and oxidation
 - Action similar to acyclovir: activated by viral thymidine kinase to inhibit viral DNA polymerase
- Activity: HSV, VZV, CMV
- Pharmacokinetics: bioavailability of penciclovir is 77%
- Adverse effects: nephrotoxicity with IV infusion, seizures
- Pregnancy category B

VALACYCLOVIR

- Mechanism of action
 - Valacyclovir (a prodrug) is the L-valine ester of acyclovir and exerts its action after being transformed into acyclovir during its first pass through the intestine and liver
- Activated by viral thymidine kinase to inhibit viral DNA polymerase
- Bioavailability is three to five times greater than acyclovir
- Activity against HSV, VZV, and CMV
- Adverse effects: nephrotoxicity with IV infusion, seizures
- Pregnancy category B

GANCICLOVIR

- Mechanism of action: nucleoside analogue that competes with deoxyguanosine for incorporation into viral DNA; hydroxymethylated derivative of acyclovir
 - Initially phosphorylated by virus-encoded kinases
 - Ganciclovir triphosphate competitively inhibits herpes virus DNA polymerase and inhibits elongation of the nascent DNA chain
 - HSV and VZV with thymidine kinase deficiency or with viral DNA polymerase mutations may be resistant to ganciclovir
- Activity: more active than acyclovir against CMV, especially CMV retinitis in immunocompromised patients
- Adverse effects: mucositis, hepatic dysfunction, seizures, granulocytopenia and thrombocytopenia; may not be totally reversible after cessation
- Pregnancy category C

VALGANCICLOVIR

- Acts as a prodrug for ganciclovir; converted to active drug by intestinal and hepatic esterases
- Adverse effects: similar to parent compound
- Activity: CMV retinitis in patients with AIDS
- Pregnancy category C

FOSCARNET

- Mechanism of action: noncompetitively inhibits viral DNA polymerase and HIV-1 reverse transcriptase by binding directly to the enzymes' pyrophosphate-binding sites
- Does not require phosphorylation for antiviral activity
- Activity: acyclovir-resistant HSV infections in AIDS patients and CMV retinitis in immunocompromised patients
- Adverse effects: nephrotoxicity, electrolyte imbalances, genital and oral ulcerations
- Pregnancy category C

AMANTADINE AND RIMANTADINE

- Mechanism of action

- Both inhibit the uncoating of viral RNA within infected host cells, thereby preventing virus replication; effective when administered orally
- Activity: influenza A and C viruses (but not influenza B), rubella
- Adverse effects: ataxia, hypertrichosis, livedo reticularis, photosensitivity, peripheral edema, alopecia, anticholinergic reactions, gastrointestinal disturbances; effects less likely with rimantidine
- Pregnancy category C

INTERFERONS (INTERFERON-A-2B)

- Mechanism of action
 - Protein product manufactured by recombinant DNA technology
 - Induces differential gene transcription; inhibits viral replication; antiviral and immunomodulatory effects by suppressing cell proliferation; direct antiproliferative effects against malignant cells and modulation of host immune response
- Adverse effects: flulike symptoms, cardiovascular arrhythmias, eyelash hypertrichosis, spastic diplegia, rhabdomyolysis
- Pregnancy category C

RIBAVIRIN

- Mechanism of action: inhibits viral RNA polymerase
- Purine nucleoside analogue that is phosphorylated by host cells
- Activity: respiratory syncytial virus (RSV), influenza A and B, measles
- Adverse effects: exanthem
- Pregnancy category X

CIDOFOVIR

- Mechanism of action: nucleoside analog of deoxycytidine monophosphate
 - Converted by host cell enzymes to cidofovir diphosphate, which competitively inhibits viral DNA polymerase
- Cidofovir is independent of thymidine kinase activation
- Adverse effects: renal toxicity (renal tubular damage), granulocytopenia may occur; with topical application, local irritation, pain
- Pregnancy category C

ZOSTAVAX VACCINE

- Live attenuated varicella-zoster virus vaccine
- Indicated for prevention of herpes zoster in patients 60 years or older
- 0.65 mL dose injected subcutaneously in the deltoid
- Pregnancy category C

HHV VACCINE

- Live attenuated vaccine given for prophylaxis of primary varicella

- Administered at 1 year of age
- For ages 12 and under: one dose
- For ages 13 and older: two doses, 1–2 months apart

Antiretroviral Agents

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

- Zidovudine (AZT, ZDV)
 - Mechanism of action: thymidine analogue; acts as a chain terminator
 - Resistance: due to mutations in the reverse transcriptase gene
 - Adverse effects: myelosuppression; results in anemias and/or neutropenia
 - Pregnancy category C
- Didanosine (ddI)
 - Mechanism: similar to zidovudine
 - Adverse effects: peripheral neuropathy and potentially fatal pancreatitis
 - Pregnancy category B
- Lamivudine (3TC), stavudine (d4T), and zalcitabine (ddC)
 - Mechanism of action: similar to zidovudine
 - Adverse effects: flulike symptoms, lipodystrophy, acneiform eruption, mucosal ulcers, pruritus, melanonychia, hyperpigmentation, eyelash hypertrichosis
 - Pregnancy category C
- Abacavir (ABC)
 - Mechanism of action: similar to zidovudine
 - Adverse effects: alcohol increases levels 41%; hypersensitivity reaction (which can be fatal)
 - Pregnancy category C
- Emtricitabine (FTC)
 - Mechanism of action: similar to zidovudine
 - Adverse effects: minimal toxicity; lactic acidosis with hepatic steatosis (rare)
 - Pregnancy category B

NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

- Nevirapine, delavirdine, efavirenz
- Bind directly to HIV-1 reverse transcriptase and non-competitively inhibit cDNA synthesis
- Adverse effects: rash is common (especially with nevirapine), Stevens-Johnson
- Pregnancy category C

PROTEASE INHIBITORS (PIs)

- Mechanism of action: inhibit HIV protease activity, blocking Gag and Gag-Pol cleavage required for assembly of progeny virions
 - Saquinavir, indinavir, nelfinavir, amprenavir, fosamprenavir, ritonavir, atazanavir, lopinavir, tipranavir, darunavir
- Adverse effects: nephrolithiasis (indinavir), abnormal fat deposits such as “buffalo hump” (indinavir),

severe diarrhea (nelfinavir), hepatotoxicity associated with concurrent use of other HIV agents and with comorbid hepatitis C, lipodystrophy, osteopenia, insulin resistance, severe lipid abnormalities, sulfa type rashes (darunavir), periungual pyogenic granulomas (indinavir)

- Pregnancy category C

NUCLEOTIDE ANALOGUES: TENOFOVIR

- Mechanism of action: inhibits reverse transcriptase
- Adverse effects: peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance; gastrointestinal complaints
- Monitor: changes in serum creatinine and serum phosphorus in patients at risk or with history of renal dysfunction
- Pregnancy category B

FUSION INHIBITORS: ENFUVIRTIDE

- Mechanism of action: binds to proteins on viral envelope and inhibits conformational change needed for fusion between viral envelope and CD4 cells
- Pregnancy category B

Antifungal Agents

ALLYLAMINES

- Mechanism of action: inhibits first step of ergosterol synthesis by blocking the activity of squalene epoxidase; fungistatic
 - Examples: butenafine, naftifine, terbinafine
- Adverse effects: hepatocellular injury, delayed gastric emptying, dysgeusia (metallic taste), reversible agranulocytosis, lupus erythematosus; terbinafine can cause gastrointestinal disturbance and nausea
- Pregnancy category B

AZOLES

- Class members
 - *Imidazoles*: azole ring contains two nitrogen atoms
 - Examples: ketoconazole, clotrimazole, miconazole
 - *Triazoles*: azole ring contains three nitrogen atoms
 - Examples: fluconazole, itraconazole, voriconazole, posaconazole
- Mechanism of action: blocks ergosterol synthesis by binding to and inhibiting the fungal CYP-450 dependent enzyme lanosterol 14- α -demethylase (converts lanosterol to ergosterol); fungistatic
- Voriconazole and posaconazole are being used for invasive fungal infections, i.e., aspergillus, fusarium
- Adverse effects:
 - Hepatitis (greatest risk with ketoconazole); congestive heart failure and hypertriglyceridemia (itraconazole)

- Ketoconazole: endocrine effects (gynecomastia, infertility, menstrual irregularities)
- Miconazole: thrombophlebitis after IV administration
- Voriconazole: visual disturbances in 30% of patients: altered/enhanced visual perception, blurred vision, color vision change, and or photophobia—effects clear after discontinuation of medication
- Drug interactions
 - Itraconazole and ketoconazole inhibits CYP 3A4
 - Fluconazole inhibits CYP 2C9; can increase INR when given with warfarin
- Pregnancy category C

POLYENES

- Amphotericin B
- Mechanism of action: binds to ergosterol and forms amphotericin B-associated membrane pores, altering the fungal membrane's permeability and causing leakage of intracellular Na^+ , K^+ , and H^+ ions, leading to cell death
- Adverse effects:
 - Amphotericin B binds cholesterol (mammalian cell membranes) to a far lesser extent than ergosterol
 - Hepatitis, infusion reactions, anemia, fever, flushing/generalized erythema, nephrotoxicity, hypotension
- Resistance: develops when binding of the drug to ergosterol is impaired or when ergosterol concentration in the membrane is decreased
- Pregnancy category B

GLUCAN SYNTHESIS INHIBITORS/ECHINOCANDINS

- Caspofungin
- IV administration
- Mechanism of action: inhibits glucan synthesis (essential polysaccharide of the fungal cell wall)
- Activity: primarily *Candida*, *Aspergillus*
- Pregnancy category C

GRISEOFULVIN

- Mechanism of action: interferes with microtubule function, causing metaphase arrest
- Produced by *Penicillium griseofulvum*
- Activity: fungistatic for dermatophytes
- Adverse effects: gastrointestinal disturbance, headaches, hypersensitivity, photosensitivity, paresthesias, hepatotoxicity, amenorrhea, exacerbation of acute intermittent porphyria (contraindicated in patients with porphyria)
- Drug interactions: griseofulvin decreases warfarin, and oral contraceptive concentrations
- Pregnancy category C

Immunosuppressive Agents

CYCLOSPORINE

- Mechanism of action
 - Binds to an immunophilin called *cyclophilin A* (CyPA) and inhibits calcineurin
 - Calcineurin regulates the transcription factor NFAT (nuclear factor of activated T cells) by dephosphorylating the cytoplasmic component (NFATc); NFATc translocates into the nucleus, where it binds NFATn
 - NFATn regulates cytokine-encoding genes, including interleukin 2 (IL-2) and interferon- γ (IFN- γ)
- Adverse effects: hypertension, hyperkalemia, hyperuricemia, hypomagnesemia, hyperlipidemia, renal toxicity, hypertrichosis, gingival hyperplasia, neurotoxicity (headache, tremor, paresthesias), lymphoma (especially in transplant patients), increased incidence of skin cancer, osteoporosis
- Monitor: chemistry panel, magnesium, lipid panel, blood pressure, lymph nodes; serum creatinine in long-term cyclosporin A therapy is a poor predictor of altered renal function (check creatinine clearance); contraindicated with PUVA
- Drug interactions: any medication that induces, inhibits, or competes for CYP 3A4 (see Table 24-1); cyclosporine can increase risk of rhabdomyolysis when used with statins
- Pregnancy category C

Immunobiologicals

ETANERCEPT

- Fully human receptor fusion protein comprised of a dimer of the p-75 external domain of tumor necrosis factor- α (TNF- α) receptor linked to the Fc portion of human IgG1
- Mechanism of action competitively binds to soluble and membrane-bound TNF- α and binds to TNF- β
- Dose: 25mg or 50 mg subcutaneous injection once or twice weekly
- Baseline CBC, CMP, LFT, and PPD recommended for all TNF- α inhibitors; some also advocate baseline ANA and chest x-ray
- Adverse effects: injection site reaction, reactivation of latent tuberculosis, multiple sclerosis and CNS demyelinating disorders, positive antinuclear antibody ANA (11%), exacerbation of or new-onset congestive heart failure (CHF) (caution use in patients with CHF)
- Relative contraindications: family history of demyelinating disease or multiple sclerosis
- Absolute contraindications: infections and known hypersensitivity
- Avoid live vaccines
- Pregnancy category B

TABLE 24-1 Examples of CYP3A4 Subfamily Substrates, Inducers, and Inhibitors*

CYP3A4 Substrates	CYP3A4 Inducers	CYP3A4 Inhibitors
Alprazolam Atorvastatin Buspirone Busulfan Cyclosporine Digoxin Didanosine Docetaxel Dofetilide Erythromycin Felodipine Fluconazole (antifungal) Glyburide Indinavir Itraconazole (antifungal) Ketoconazole (antifungal) Loratadine (antihistamine) Lovastatin (statins) Metformin Miconazole (antifungal) Midazolam Nifedipine Pimozide Prednisone Quinidine Rifampin Ritonavir Saquinavir Sildenafil Simvastatin (statins) Tacrolimus Triazolam Verapamil Vincristine Warfarin	Carbamazepine Cortisol Dexamethasone Griseofulvin Nevirapine Omeprazole Pantoprazole Phenobarbital Phenylbutazone Phenytoin Prednisone Primidone Rifabutin Rifampicin Rifampin Troglitazone	Cimetidine Clarithromycin Diltiazem Erythromycin Felfinavir Fluconazole (high dose) Fluoxetine Fluvoxamine Gestodene Grapefruit Indinavir Itraconazole Ketoconazole Miconazole Mibefradil Nefazodone Nifedipine Omeprazole Propoxyphene Ritonavir Saquinavir Verapamil
<p>* This is not a complete list, and readers should refer to the manufacturer's individual package insert for current information.</p> <p>From Freedberg IM et al: Fitzpatrick's Dermatology in General Medicine, 6th ed. New York: McGraw-Hill; 2003, p. 2445.</p>		

INFLIXIMAB

- Mouse-human chimeric IgG1 monoclonal antibody specific for TNF- α (human antibody constant regions and murine antibody variable region)
- Mechanism of action: binds to TNF- α only and inhibits its binding to soluble and transmembrane TNF- α receptors
- IV infusion 3–10 mg/kg, 4- to 8-week intervals
- Adverse effects: infusion reactions, risk of serious infections, reactivation of tuberculosis, positive ANA, serum sickness, hepatotoxicity, rare pancytopenia, malignancy risk, CNS demyelinating disorders, exacerbation of or new-onset CHF
- Anti-drug antibodies to the chimeric portion can form and reduce efficacy

- CHF and family history of demyelinating disease or multiple sclerosis are relative contraindications; infections and known hypersensitivity are absolute; avoid live vaccines
- Pregnancy category B

ADALIMUMAB

- Fully human IgG1 monoclonal antibody to TNF- α only
- Mechanism of action: blocks TNF- α interaction with the p55 and p75 transmembrane TNF receptor
- Dose: subcutaneous injection 40 mg every other week
- Adverse effects: injection site reactions, increased rate of infection in clinical trials, positive ANA, demyelinating disorders, malignancy, exacerbation of or new-onset CHF
- Contraindications same as etanercept; avoid live vaccines
- Pregnancy category B

EFALIZUMAB

- Humanized IgG1 monoclonal antibody against human CD11a subunit of leukocyte function antigen-1 (LFA-1)
- Mechanism of action: blocks the interaction of LFA-1 on T cells with intercellular adhesion molecule 1 (ICAM-1) on antigen presenting cells
- Subcutaneous injection weekly; weight based with conditioning dose
- Adverse effects: thrombocytopenia, psoriasis-like eruption during administration and rebound of psoriasis after discontinuation, hypersensitivity reaction, anti-drug antibodies, rare LFT elevation
- Monitor platelet counts monthly (discontinue if platelets < 100,000); no live or acellular vaccines
- Pregnancy category C
- No longer available due to possible risk of progressive multifocal leukoencephalopathy (PML)

ALEFACEPT

- Fully human dimeric fusion protein of LFA-3 linked to the Fc portion of human IgG1
- Mechanism of action: blocks the interaction of LFA-3 on antigen presenting cells with CD2 on T cells (mostly memory CD45RO+ cells)
- Also links CD2 with CD16 (Fc γ III receptor) on natural killer cells triggering apoptosis of selected memory T cells expressing high levels of CD2 on the surface
- Intramuscular injection given weekly for 12 weeks, followed by 12-week observation period
- Adverse effects: lymphopenia with low CD4 (greatest at 6–8 weeks), malignancies (most commonly skin cancer), infections, hypersensitivity reactions, injection-site reactions, increased LFTs, anti-drug antibodies
- Monitoring: CD4+ T-lymphocyte counts should be monitored weekly during the 12-week dosing period;

dose should be held if CD4+ T-lymphocyte counts fall below 250 cells/ μ l; medication should be discontinued if counts remain below 250 cells/ μ l for 1 month

- Pregnancy category B

USTEKINUMAB

- Fully human monoclonal antibody targeting p40 subunit of interleukin-12 (IL-12) and interleukin-23 (IL-23)
- 45 mg or 90 mg subcutaneous injection at weeks 0, 4, and then every 12 weeks.
- Approved for the treatment of moderate to severe psoriasis

DENILEUKIN DIFTITOX

- Mechanism of action
- Diphtheria toxin and the receptor-binding domain of human IL-2 are fused
- Drug binds to the IL-2 receptor [cluster of differentiation 25 (CD25)]
- Internalized by receptor-mediated endocytosis and inhibits protein synthesis by translocation of the active portion of diphtheria toxin into the cytosol
- 50% of patients with mycosis fungoides or Sézary syndrome have malignant cells that express CD25; patient's malignant cells should be tested for CD25 expression to see if this medication would be helpful
- Adverse effects: hypersensitivity/vascular leak syndrome: if two or more of the following three symptoms are present: hypotension, edema, and hypoalbuminemia; common during the first 2 weeks of infusion and may persist or worsen after completing treatment; hypoalbuminemia: occurs after 1 to 2 weeks (serum albumin levels should be at least 3.0 g/d); infectious complications; hypersensitivity
- Pregnancy category C

THALIDOMIDE

- Mechanism of action: TNF- α and IL-12 suppressor, antiangiogenic; downregulates adhesion molecules
- Drug of choice for erythema nodosum leprosum
- Adverse effects: sedation, constipation, peripheral (sensory) neuropathy, teratogenicity, leukopenia, bradycardia, rash and fever (mainly in HIV patients), severe birth defects; malformations of extremities, microphthalmia, neural tube defects, cardiac and renal malformations, esophageal fistulas, duodenal atresia, vaginal obstruction
- Monitoring: baseline and monthly neurologic examinations; CBC
- Serum pregnancy testing 24 hours prior to starting medication, then every week for the first month, then monthly thereafter; contraception, testing, and drug therapy compliance survey by patient
- Drug interactions: additive sedative effects: alcohol, barbiturates, chlorpromazine, reserpine

- Antagonized by thalidomide: acetylcholine, histamine, prostaglandins, serotonin
- Pregnancy category X

Antimycobacterial Agents

ISONIAZID

- Mechanism of action: disrupts mycobacterial cell walls, inhibits mycolic acid synthesis
- Bacteriostatic at most concentrations
- Elimination through acetylation
- Fast and slow acetylation of patient affects elimination half-life: fast = 70 minutes, slow = 180 minutes
- Adverse effects: neurotoxic, hepatotoxic, hemolysis in G6PD deficiency, lupus erythematosus, acneiform eruption, onycholysis, pellagra-like eruption, photosensitivity, pyridoxin (B₆) deficiency with high doses
- Pyridoxine supplementation can decrease risk of peripheral neuritis
- Pregnancy category C

RIFAMPIN

- Mechanism of action
- Macrocytic antibiotic derived from *Streptomyces mediterranei*
- Mechanism of action: bactericidal; inhibits DNA-dependent RNA polymerase, interfering with bacterial RNA synthesis
- Activity: *Mycoplasma tuberculosis*, many gram-negative organisms, many chlamydiae
- Adverse effects: orange-red discoloration of skin, urine, tears; glossodynia; increased risk of deep venous thrombosis; anti-drug antibodies; IgE mediated anaphylaxis
- Monitoring: CBC and LFT at baseline and during therapy; interruption of therapy and high-dose intermittent therapy associated with thrombocytopenia (reversible if therapy is discontinued as soon as purpura occurs)
- Rifabutin: semisynthetic rifampin that is more effective in treating atypical mycobacteria
- Drug interactions: potent inducer of multiple CYP enzymes
- Pregnancy category C

CLOFAZIMINE

- Red, fat-soluble, crystalline dye
- Mechanism of action: inhibits mycobacterial growth by binding preferentially to mycobacterial DNA
- Adverse effects: skin discoloration; secretions discolored: red urine; ichthyosis; severe abdominal symptoms, splenic infarction (rare), bowel obstruction, and gastrointestinal bleeding; crystalline deposits of clofazimine in tissues, including

intestinal mucosa, spleen, liver, and mesenteric lymph nodes

- Pregnancy category C

ETHAMBUTOL

- Mechanism of action: inhibits metabolite synthesis in susceptible bacteria, resulting in impaired cellular metabolism and cell death
- Bacteriostatic
- Useful for organisms resistant to streptomycin and isoniazid (no cross-resistance)
- Adverse effects: dose-dependent visual disturbances, neurotoxicity, hyperhidrosis, gout
- Pregnancy category C

PYRAZINAMIDE (PZA)

- Mechanism of action: unknown
- Bacteriostatic or bactericidal against *M. tuberculosis* depending on concentration of drug attained at site of infection
- Adverse effects: photosensitivity, myalgias, hyperuricemia, gastrointestinal irritation, red-brown change in skin color, alopecia, flushing, hepatic injury (most common and serious side effect); gout can be precipitated by inhibition of excretion of urate
- Pregnancy category C

STREPTOMYCIN

- Mechanism of action
- Bactericidal antibiotic; interferes with normal protein synthesis
- Added as a fourth drug for *M. tuberculosis* treatment
- Given by injection
- Adverse effects: renal tubular damage, vestibular damage, and ototoxicity; caution with myasthenia gravis, hypocalcemia, and conditions that depress neuromuscular transmission
- Pregnancy category D

Miscellaneous

PENICILLAMINE

- Mechanism of action
- Metal chelator used to treat arsenic poisoning; historical usage for scleroderma
- Adverse mucocutaneous effects: elastosis perforans serpiginosa, bullous diseases (pemphigus, pemphigoid), drug induced lupus, pseudoxanthoma elasticum, and lichen planus
- Pregnancy category D

COLCHICINE

- Mechanism of action: binds to tubulin dimers in neutrophils and inhibits microtubule assembly needed in metaphase; antimitotic

- Adverse effects: dose-dependent gastrointestinal symptoms of cramping and watery diarrhea common; overdose can cause renal failure, hepatic failure, permanent hair loss, bone marrow suppression, numbness or tingling in hands and feet, disseminated intravascular coagulopathy, decreased sperm count
- Pregnancy category C (parenteral D)

POTASSIUM IODIDE

- Mechanism of action: unknown; may inhibit granuloma formation and suppress delayed type hypersensitivity reactions by releasing heparin from mast cells
- Used to treat sporotrichosis, erythema nodosum, subacute nodular migratory panniculitis
- Adverse effects: hypothyroidism from Wolff-Chaikoff effect (excess iodide blocks organic iodide binding in thyroid hormone synthesis); iododerma, acneiform, and vascular eruptions; flare-up of dermatitis herpetiformis
- Pregnancy category D

AURANOFIN

- Mechanism of action: gold is taken up by macrophages, which in turn inhibit phagocytosis and lysosomal membrane stabilization
- Alters immunoglobulins, decreasing prostaglandin synthesis and lysosomal enzyme activity
- Monitor: discontinue therapy if platelet counts fall to less than 100,000/mm³, white blood cell count to less than 4000/mm³, granulocytes to less than 1500/mm³
- Pregnancy category C

INTRAVENOUS IMMUNOGLOBULINS (IVIg)

- Immunoglobulins are extracted from pooled plasma requiring between 10,000 and 20,000 donors
- Mechanism of action: blockade of Fc receptors, prevents complement mediated effects, reduces circulating pathogens and antibodies, alters cytokine/cytokine antagonist ratios
- Adverse effects: increases in creatinine and blood urea nitrogen, infusion reaction (within one hour) headache, flushing, chills, myalgia, wheezing, tachycardia, low back pain, nausea, and/or hypotension.
- Monitor: LFT's, renal function tests, immunoglobulin levels (in order to exclude IgA deficiency), rheumatoid factor and cryoglobulin levels, screen for HIV and hepatitis
- Contraindications: documented hypersensitivity; IgA deficiency; anti-IgE/IgG antibodies
- Pregnancy category C

SPIRONOLACTONE

- Mechanism of action: aldosterone antagonist, weak antiandrogen activity by blocking androgen receptor and by inhibiting androgen biosynthesis; may be converted by progesterone 17-hydroxylase to active metabolites that decrease testosterone and dihydrotestosterone (DHT) production.
- Clinical use: dermatologic uses are off label and include acne vulgaris, androgenetic alopecia, hirsutism, hidradinitis suppurativa
- Adverse effects: menstrual irregularities, hyperkalemia, hyponatremia, potential teratogenicity as an antiandrogen (feminization of a male fetus)
- Monitor: serum androgens (testosterone, dehydroepiandrosterone (DHEAS) if abnormal at baseline, periodic serum potassium
- Contraindications: renal insufficiency, anuria, hyperkalemia, pregnancy, abnormal uterine bleeding, family or personal history of estrogen dependent malignancy
- Drug interactions: increased potential of hyperkalemia: angiotensin-converting enzyme inhibitors, thiazide diuretics, potassium supplements
- Increased levels of digoxin if taken with spironolactone
- Pregnancy category X

PHOTOTHERAPY

- Ultraviolet B (UV-B): 290–320 nm
- Narrow band UV-B (311 nm)
- Goeckerman regimen: coal tar followed by UV-B exposure
- Ingram method: anthralin application following a tar bath and UV-B treatment
- Psoralen and ultraviolet A (wavelengths 320–400 nm) photochemotherapy (PUVA)
- Mechanism of action:
 - Uses the photosensitizing drug methoxsalen (8-methoxypsoralen) in combination with ultraviolet A (UV-A) irradiation
 - Interferes with DNA synthesis by inhibiting mitosis and binding covalently to pyrimidine bases in DNA when photoactivated by UV-A
 - Decreases cellular proliferation, and also induces apoptosis of cutaneous lymphocytes leading to a localized immunosuppression
- Adverse effects of PUVA therapy: nausea, pruritus, and burning; known to be carcinogenic, with risk being dose-dependent; minimize exposure to outdoor or bright indoor light for 24 hours after each dose due to photosensitivity; PUVA lentiginos
- Contraindications: diseases associated with photosensitivity
- Pregnancy category C

TOPICAL TREATMENTS

Vehicles in Dermatologic Therapy

Combination of various chemicals to enhance the usability of the treatment

- Common vehicle ingredients:
 - *Emollients*: used to retard transepidermal loss, occlude the active molecule, increase flexibility of the skin. (i.e. glycerin, petrolatum, mineral oil, stearic acid, propylene glycol stearate)
 - *Emulsifying agents*: help create oil-in-water preparations: cream and lotions. (i.e. lanolin, sodium lauryl sulfate)
 - *Solvents*: help to create a less viscous product (i.e. alcohol, propylene glycol)
 - *Humectants*: used in all oil-in-water preparations to maintain the required water content (i.e. glycerin, propylene glycol)
- Types of vehicles:
 - *Cream*: a semisolid emulsion of oil in water; contains a preservative to prevent overgrowth of microorganisms; stabilized by an aqueous emulsifier
 - *Gel*: a semisolid, transparent, nongreasy emulsion (cellulose cut with alcohol or acetone)
 - *Lotion*: liquid vehicle, aqueous or alcohol-based, that may contain a salt in solution
 - *Ointment*: a semisolid grease/oil, sometimes also containing powder, but little or no water; the active ingredient is suspended; usually no preservative needed
 - *Paste*: an ointment with a high proportion of powder that gives a stiff consistency
- Other vehicles:
 - Foam
 - Hydrogel: (alcohol and surfactant free)

Acne Preparations

BENZOYL PEROXIDE

- Mechanism of action: broad spectrum bactericidal agent with oxidizing activity
- Activity against: *P. acnes*, *S. capitis*, *S. epidermidis*, *S. hominis*, *P. avidum*, *P. granulosum* and *Pityrosporum ovale*
- Antibacterial effect greater than comedolytic effects
- Adverse effects: skin irritation and drying; contact allergy (1 %)

AZELAIC ACID

- Dicarboxylic acid
- Mechanism of action
 - Reduces production of keratin and inhibits growth of *Propionibacterium acnes*, antityrosinase activity
- Adverse effects: may produce hypopigmentation, skin irritation
- Pregnancy category B

SALICYLIC ACID

- Keratolytic
- Adverse effects: erythema and peeling,
- Systemic toxicity (occurs when blood concentrations exceed 35 mg/dl) nausea, vomiting, confusion, dizziness, delirium, psychosis, stupor, coma, death, respiratory alkalosis, metabolic acidosis, hypoglycemia, tinnitus, hyperventilation

SULFUR

- Comedolytic, keratolytic, mild antibacterial dose 5–10 %
- Adverse effects: odor, application site reaction
- Lotion 5 % sulfur, 22 % alcohol
- Combination: sulfur–sodium sulfacetamide
- Lotion 50 mg sulfur, 100 mg sulfacetamide

RETINOIDS

- Mechanism of action: see systemic section for details
- *Tretinoin (all-trans retinoic acid)*
 - Binds with approximately equal affinity to all three RARs and also can be converted to forms that activate the RXRs
 - Adverse effects: tenderness, erythema, and burning; also increased risk of sunburn
 - Pregnancy category C
- *Adapalene*
 - Retinoid properties from a synthetic naphtholic acid derivative
 - Equal selectivity for the nuclear RAR- β/γ receptors (RAR- γ predominant receptor in epidermis) and weakly for RAR- α
 - Pregnancy category C
- *Tazarotene*
 - Prodrug is hydrolyzed rapidly in tissues to the active metabolite tazarotenic acid
 - Binds to RAR- $\beta >$ RAR- $\gamma >$ RAR- α receptors, no RXR
 - Pregnancy category X
- *Alitretinoin (9-cis-retinoic acid)*: binds to and activates both RXRs and RARs, all subtypes; used for Kaposi's sarcoma

Alpha-Hydroxy Acids (See Chapter 14)

Topical Antibiotics

See above for mechanisms of other antibiotics.

MUPIROICIN

- Produced by fermentation of *Pseudomonas fluorescens*
- Mechanism of action: inhibits bacterial isoleucyl-tRNA synthetase and blocks bacterial RNA synthesis
- Pregnancy category B

RETAPAMULIN

- Belongs to the pleuromutilin class

- Mechanism of action: inhibits the initiation of protein synthesis at the level of bacterial 50S ribosome; bacteriostatic
- Pregnancy category B

SILVER SULFADIAZINE

- Mechanism of action: inhibiting DNA replication and modification of the cell membrane adverse effects—early leukopenia (in post burn patients)

DAPSONE

- Sulfone derivative with anti-inflammatory properties
 - Mechanism of action: see systemic section above
 - 5% gel applied twice daily
 - Indicated for acne
 - Adverse events: oiliness, peeling, dryness, erythema at the application site, no cross reactivity with sulfonamides (antimicrobial agents)
 - Pregnancy category C

Bleaching Agents

HYDROQUINONE

- Inhibits tyrosinase (causes oxidation of tyrosine to 3, 4-dihydroxyphenylamine)
- Prepared 2%, 3%, and 4% concentrations
- Adverse events: exogenous ochronosis
- Pregnancy category C

KOJIC ACID

- Mechanism of action: inhibits tyrosinase
- Adverse effects: contact sensitivity

MEQUINOL

- Mechanism of action: exact action unknown; it is a substrate for tyrosinase, and thus, a competitive inhibitor of the formation of melanin precursors
- Pregnancy category X when used with tretinoin

Topical Anesthetics (See Chapters 13 and 14)

- Topical Immunosuppressives

TACROLIMUS AND PIMECROLIMUS

- Macrolide derived from *Streptomyces tsukubaensis*
- Mechanism of action
 - Binds to FK-506 binding protein (receptor within cytoplasm) and the drug-protein complex inhibits calcineurin (a calcium-dependent phosphatase enzyme)
 - Without the phosphatase activity of calcineurin, nuclear factor of activated T-cells (NF-AT) cannot translocate to the nucleus and activate transcription of proinflammatory cytokines
 - IL-2, IL-3, IL-4, IL-5, IL-10, GM-CSF, and TNF- α

- Reduction in the activity of T-lymphocytes in the immune system
- Adverse effects: minimally absorbed into the blood; application site stinging
- Pregnancy category C

Topical Antivirals

IMQUIMOD 5% CREAM

- Imidazoquinoline amine
- Mechanism of action
 - Induction of cytokines after binding to a transmembrane receptor: Toll-like receptor 7 (an innate immunity response)
 - Stimulation of the cellular arm of acquired immunity through induction of IFN- α , IFN- γ , and IL-12; T memory cells are created after activation from dendritic cells
- Adverse effects: local skin irritation
- Pregnancy category C

ACYCLOVIR, PENCICLOVIR

- Mechanism of action and side effects: See oral section

PODOPHYLLIN

- Extract from May apple plant
- Mechanism of action: binds to protein tubulin and arrests cells in metaphase; antimitotic
- Pregnancy category X

Antifungals

ZINC PYRITHIONE

- Mechanism of action: inhibitor of membrane transport in fungi
- Adverse effects: allergic contact dermatitis
- Azoles, allylamines, polyenes: see oral section

SELENIUM SULFIDE

- Mechanism of action: increase fungal shedding by decreasing comeocyte production; sporocidal
- Adverse effects: skin irritation, hair loss

CICLOPIROX

- Mechanism of action: chelation of polyvalent metal cations (e.g., Fe³⁺ and Al³⁺); inhibits metal-dependent enzymes, responsible for the degradation of peroxides within microbial cells
- Adverse effects: contact dermatitis and pruritus
- Pregnancy category B

Androgenetic Alopecia Treatment

MINOXIDIL

- Mechanism of action
- Relaxes arteriolar smooth muscle, causing vasodilation; mechanism for hair growth not known

- Adverse effects: may exacerbate angina pectoris; caution in pulmonary hypertension, congestive heart failure, coronary artery disease, and significant renal failure
- Pregnancy category C

FINASTERIDE

- Mechanism of action: inhibits conversion of testosterone to dihydrotestosterone by inhibiting competitive inhibition of type II 5 α -reductase
- Adverse effects: decreased libido or erectile dysfunction (2%)
- Pregnancy category X

Treatment of Hirsutism

EFLORNITHINE HCL 13.9% CREAM

- Mechanism of action: inhibits enzyme ornithine decarboxylase (ODC)
- Metabolic activity in the hair follicle decreases, and hairs grow in more slowly
- Adverse effect: mild skin irritation
- Pregnancy category C

Sunscreens

- Chemical Blockers
- Aromatic compounds conjugated with a carbonyl group

ULTRAVIOLET B FILTERS

- *Aminobenzoic acid and derivatives*
 - Padimate O (most potent UV-B absorber)
 - *para*-Aminobenzoic acid (PABA): high incidence of hypersensitivity
- Cross-sensitivity with PABA: artificial sweeteners (e.g., saccharin, sodium cyclamate); ester-type anesthetics, Azo dyes (e.g., aniline, paraphenylenediamine), sulfonamide antibiotics, sulfonamide-based oral hypoglycemics, or thiazide diuretics
- *Cinnamates*
 - Octyl methoxycinnamate (second most potent UV-B absorber compared with padimate O)
 - Cross sensitivity to cinnamon derivatives: balsam of Peru, balsam of Tolu, Cassia, cinnamic acid, cinnamic alcohol, cinnamic aldehyde, cinnamon oil, coca leaves
- *Salicylates*
 - Octyl salicylate: used to augment the UV-B protection in a sunscreen, 280–320 nm
 - Weak UV-B absorbers
- *Octocrylene*
 - May be used in combination with other UV absorbers, 250–360 nm
 - Phenylbenzimidazole sulfonic acid, selective UV-B filter

ULTRAVIOLET A FILTERS

- *Benzophenones oxybenzone*, absorbs well through UV-A II (benzophenone-3) wavelengths,

benzophenones are primarily UV-B absorbers, 270–350 nm

- *Anthranilates*: menthyl anthranilate, absorbs mainly in the near UV-A portion, 260–380 nm
- *Dibenzoylmethanes*
 - Avobenzone (Parsol 1789), 320–400 nm
 - Dioxybenzone, 250–390 nm
 - Mexoryl

PHYSICAL BLOCKERS

- *Titanium dioxide*, 290–700 nm
- *Zinc oxide*, 290–700 nm

Parasiticidals

MALATHION

- Mechanism of action: irreversible cholinesterase inhibitor hydrolyzed (and therefore detoxified) rapidly by mammals, but not by insects
- Binds to hair and may provide some residual protection after therapy
- Adverse effects: alcohol may irritate excoriated skin; the lotion is flammable; take care to avoid mucosal surfaces, eyes; do not apply to lashes
- Pregnancy category B

PERMETHRIN

- Mechanism of action: synthetic pyrethrin
- Neurotoxin that causes paralysis and death in ectoparasites
- Adverse effects: lack of safety data on children younger than 2 months as well as pregnant and breast-feeding women
- Pregnancy category B

LINDANE 1% (GAMMA-BENZENE HEXACHLORIDE)

- Mechanism of action: neurotoxin that causes seizures and death in parasitic arthropods
- Adverse effects: do not use in infants, small children, patients with a history of seizure, or lactating or pregnant women

PRECIPITATED SULFUR 6%

- Topical formulation can be used to treat scabies in pregnant women and young infants

CROTAMITON

- 10% cream or lotion
- Indicated for scabies
- Mechanism: unknown
- Pregnancy category C

Topical Corticosteroids

- Mechanism of action: see systemic section for details
- Efficacy of an individual topical corticosteroid is related to its potency (the intensity of a TCS's clinical effect)
- Pharmacokinetics: clinical potency of a TCS preparation depends on three factors: structure, vehicle, and

type of skin to which it is applied. The addition of functional groups (e.g., hydroxy, hydrocarbon, ester, fluoro, chloro, acetone, ketone)

- Hydroxyl group changes: affects lipophilicity, solubility, percutaneous absorption, glucocorticoid receptor (GCR)-binding activity.
- Halogenation: augments glucocorticoid and mineralocorticoid activity
- Fluorination or chlorination: enhances potency
- Class 1: superpotent
- Classes 2 and 3: high
- Classes 4 and 5: intermediate
- Class 6: low
- Class 7: least potent
- Adverse effects: local: acne, tachyphylaxis, skin atrophy (striae, telangiectasia and purpura), glaucoma/cataracts, delayed wound healing, allergic dermatitis, tachyphylaxis, systemic: may suppress hypothalamic-pituitary-adrenal (HPA) axis (rare)
- Risk factors for adverse effects: young age, liver disease, renal disease, amount of topical steroid applied, potency of topical steroid, use of occlusion, location of topical application (face, neck, axilla, groin, upper inner thighs)

Topical Corticosteroid Allergic Contact Dermatitis Cross-Reaction Groups

- *Group A*: hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisolone, methylprednisolone, prednisone
- *Group B*: triamcinalone acetate, triamcinalone alcohol, amcinonide, budesonide, desonide, fluocinonide, fluocinolone acetate, halcinonide
- *Group C*: betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, fluocortolone
- *Group D*: hydrocortisone-17-butyrate, hydrocortisone-17-valerate, acemetasone dipropionate, betamethasone dipropionate, prednicarbate, clobetasone-17-butyrate, clobetasol-17-propionate, fluocortolone caproate, fluocortolone acetate.
- Screening agents for patch testing: tixocortol pivalate, hydrocortisone-17-butyrate, budesonide.

Topical Chemotherapy Agents

NITROGEN MUSTARD

- Mechanism of action: cytotoxic to cancer cells via DNA alkylation
- Adverse effects: delayed hypersensitivity (35% to 60%), can be overcome with use of topical steroids or desensitization and less common with use of ointment; associated with an increased risk of non-melanoma skin cancers
- Pregnancy category D

5-FLUOROURACIL

- Mechanism of action: inhibits thymidylate synthetase, leading to inhibition of DNA synthesis and cell death
- Adverse effects: local pain, pruritus, hyperpigmentation, irritation, inflammation and burning at the site of application, allergic contact dermatitis, scarring, soreness, tenderness, suppuration, scaling and swelling
- Pregnancy category D

Other

CASTELLANI PAINT

- Compound solution of resorcinol (8 g), acetone (4 ml), magenta (0.4 g), phenol (4.0 g), boric acid (0.8 g), industrial methylated spirit 90% (8.5 ml), and water (100 ml)
- Fungicidal and bactericidal
- Adverse effects: magenta can stain clothing and skin; may be toxic in children because of phenol content; may cause irritation
- Pregnancy category C

PHOTODYNAMIC THERAPY (PDT)

- Mechanism of action
 - Topical application of aminolevulinic acid (ALA) on skin leads to the accumulation of the endogenous photosensitizer protoporphyrin IX (PpIX) in epidermal cells
 - Conversion of ALA to PpIX occurs in skin cells by enzymes in the heme biosynthetic pathway
 - Rapidly proliferating skin cells convert more ALA to PpIX than do less rapidly proliferating normal epidermal cells
 - Subsequent illumination of the lesion with noncoherent blue light (417 nm) 3 to 6 hours after ALA application causes ALA to be enzymatically converted into the active endogenous photosensitizer PpIX
- Methyl 5-aminolevulinate also can be used instead of ALA with red light (630nm); other light sources are between 400–800nm (visible spectrum) and include pulsed dye laser and intense pulsed light
- Apoptotic cell death and vascular injury for PDT-mediated tissue ablation
- Adverse effects: burning pain, stinging, or itching restricted to the illuminated area; erythema and mild edema of the treated area; generalized cutaneous photosensitivity, photophobia, and/or ocular discomfort, residual hyperpigmentation and hypopigmentation
- Pregnancy category C

CALCIPOTRIENE (CALCIPOTRIOL)

- Mechanism of action
 - Synthetic analog of calcitriol. Vitamin D has been shown to inhibit the proliferation of keratinocytes

- in culture and to modulate epidermal differentiation; vitamin D inhibits production of IL-2 and IL-6 by T cells, blocks transcription of interferon (IFN)-gamma and granulocyte-macrophage colony-stimulating factor (GM-CSF), messenger ribonucleic acid (mRNA) and inhibits cytotoxic and natural killer T cell activity.
- Adverse effects: hypercalcemia: use should not exceed 100 g per week
- Pregnancy category C

ANTHRALIN

- Mechanism of action
 - Naturally occurring saturated dicarboxylic acid—possessing antibacterial, comedolytic, and anti-inflammatory activities
 - Stimulates monocytes proinflammatory activity and induces extracellular generation of free radicals
 - Inhibits cell growth and restores cell differentiation
- Prolonged contact method uses 0.5%–1.0% preparations applied for several hours; short contact method uses higher concentrations of anthralin (0.5%–1.0%) but usually applied for only 1 hour or less
- Adverse effects: irritating to normal skin
- Applications in excessive amounts may stain clothing; long-term corticosteroid treatment withdrawal may cause complications of rebound phenomenon
- Pregnancy category C

Antiperspirants

ALUMINUM SALTS

- Mechanism of action: reversibly inhibits eccrine gland secretion by an unknown mechanism.
- Aluminum chloride 10% to 30% in distilled water or 60% alcohol
- Adverse effects: irritant dermatitis
- Pregnancy category C

Botulinum Toxin

- See Chap. 14.

PREGNANCY CATEGORIES

- All drugs are classified into the following categories
 - A. Controlled studies show no risk
 - Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to fetus
 - B. No evidence of risk in humans
 - Either animal findings show risk but human findings do not, or if no adequate human studies have been done, animal findings are negative
 - C. Risk cannot be ruled out

- Human studies are lacking, and the animal studies are either positive for fetal risk or lacking. However, potential benefits may justify the potential risk
- D. Positive evidence for risk
 - Investigational or postmarketing data show risk to fetus. Nevertheless, potential benefits may outweigh the potential risk
- X. Contraindicated in pregnancy
 - Studies in animals or humans or investigational or postmarketing reports have shown fetal risk that clearly outweighs any possible benefit to the patient

DRUG SIDE EFFECTS

- Acanthosis nigricans*: NODES: nicotinic acid/niacin, oral contraceptives, dilantin, estrogens, steroids
- Acne (pimples)*: phenytoin, Isoniazid, iodides, moisturizers, phenobarbital, lithium, ethionamide, steroids
- Acral erythema*: Ara-C, bleomycin, doxorubicin, etoposide, 5-FU, hydroxyurea, mercaptopurine, methotrexate
- Acral sclerosis*: bleomycin
- Acute generalized exanthematous pustulosis*: penicillin, macrolide antibiotics, alopecia, chemotherapy agents, anticoagulants, hormones, anticonvulsants, amantidine, captopril, cholesterol-lowering drugs, isotretinoin, ketoconazole, propranolol, cimetidine
- Blue-gray hyperpigmentation*: desipramine, amiodarone, antimalarials/anticonvulsants, minocycline, imipramine, thiorazine
- Bullous eruptions*: lasix, penicillamine, thiols (captopril), penicillin, sulfonamides. PUVA
- Cutis laxa*: penicillin
- Dental abnormalities*: tetracycline (gray, discolored teeth)
- Dermatomyositis*: hydroxyurea, penicillamine
- Elastosis perforans serpiginosa*: penicillamine
- Erythema nodosum*: OCP, antibiotics (sulfonamides, tetracycline, penicillin), 13-*cis* retinoic acid, gold, opiates, halogens
- Eyelash growth*: interferon, lumigan
- Fixed drug eruptions*: NSAIDs (pigmented), sulfonamides (pigmented), pseudoephedrine (nonpigmented), phenolphthaleine laxatives, OCP, tetracycline, aspirin, barbiturates, carbamazepine
- Gingival hyperplasia*: calcium channel blockers, cyclosporine, dilantin
- Gray baby syndrome*: chloramphenicol
- Hypertrichosis*: cyclosporine (but not Prograf), diazoxide, danazol, minoxidil, spironolactone, psoralen

- *Ichthyosis*: nicotinic acid
- *Leg ulcers*: hydroxyurea
- *Lichenoid eruptions*: lasix, penicillamine, gold, thiazides, chlorpropamide, antimalarials, methyldopa, phenylthiazides, beta blockers
- *Linear IgA*: vancomycin
- *Lipodystrophy*: crixivan (“crix belly”)
- *Livedo reticularis*: quinidine (photodistributed), amantadine
- *SCLE*: D-penicillamine, HCTZ, lamisil, sulfonureas, griseofulvin, naproxen, diltiazem, procainamide, PUVA, minocycline
- *Systemic lupus erythematosus (D-CHIPS)*: dilantin, chlorpropamide, hydralazine, isoniazid, procainamide, sprouts (alfalfa sprouts/L-canavanine)
- *Melanonychia striata*: AZT (zidovudine), neutrophilic eccrine hidradenitis, Ara-C, bleomycin
- *Optic neuritis*: ethambutol
- *Pellagra-like eruption*: isoniazid, azathioprine, 5-FU
- *Pemphigus vulgaris*: penicillamine, thiols (captopril)
- *Penile ulcers*: foscarnet
- *Photoallergic drug reaction*: griseofulvin, NSAIDs, phenothiazines, quinidine, sulfonamide, sulfa drugs, thiazide diuretics, *para*-amino benzoic acid, *para*-phenylene diamine
- *Photo-onycholysis*: tetracycline, 8-MOP
- *Phototoxic drug reaction*: amiodarone, nalidixic acid, NSAIDs, phenothiazines (chlorpromazine), tetracyclines
- *Pityriasis rosea-like eruptions*: barbiturates/bismuth, omeprazole, beta blockers, captopril, clonidine, griseofulvin, isotretinoin, metronidazole, penicillin
- *Porphyria cutanea tarda*: griseofulvin, rifampin, antimalarials/alcohol, busulfan/benzenes, hormones, iron, phenols, sulfonyleurea
- *Pseudolymphoma*: anticonvulsants (dilantin, phenobarbital), antihypertensives (beta blockers, ACE inhibitors, calcium channel blockers), tricyclic antidepressants, allopurinol
- *Pseudomembranous colitis*: clindamycin
- *Pseudoporphyria*: tetracycline, isotretinoin, naproxen, nalidixic acid, piroxicam, lasix, sulfonamides, hemodialysis for chronic renal failure
- *Pseudotumor cerebri*: isotretinoin, tetracycline, steroids
- *Pseudoxanthoma elasticum*: penicillamine
- *Psoriasis*: GCSF, INH, NSAIDs, steroids, lithium, ACE inhibitors/antimalarials, beta blockers, penicillamine, OCP
- *Pulmonary fibrosis*: methotrexate, interferon- α , gold, azathioprine, cyclophosphamide, cytoxan, bleomycin
- *Raynaud’s*: bleomycin, vincristine
- *Red-orange body fluids (tears/urine)*: rifampin

- *Sweet’s syndrome*: filgrastim, OCP, minocycline, all trans retinoic acid, TMP-SMZ, celecoxib
- *Toxic epidermal necrolysis*: sulfonamides, penicillin, allopurinol, NSAIDs, anticonvulsants (phenytoin, phenobarbital, carbamazepine), pentamidine
- *Urticaria*: aspirin, NSAIDs, antibiotics (penicillin, sulfonamides, rifampin, vancomycin), opiates, barbiturates, contrast dye, ACE inhibitors (captopril)
- *Vasculitis*: ampicillin, sulfonamides, thiazides, furosemide, NSAIDs, cimetidine, ACE inhibitors
- *Vestibular toxicity*: aminoglycosides

QUIZ

Questions

- Match the following medication with the enzyme it inhibits.

A. Methotrexate	i. Dihydropteroate synthetase
B. Dapsone	ii. Dihydrofolate reductase
C. Sulfonamides	
D. Trimethoprim	
- The following adverse effects of corticosteroids are not reduced by alternate day dosing EXCEPT:
 - Osteoporosis
 - Osteonecrosis
 - Adrenal crisis
 - Cataracts
- The following medications can cause increased myelosuppression when given with azathioprine EXCEPT:
 - Folate antagonists
 - Beta blockers
 - ACE inhibitors
 - Allopurinol
- Which of the following cytotoxic agents can cause reproductive side effects including azoospermia and amenorrhea?
 - Cyclophosphamide
 - Chlorambucil
 - Mycophenolate mofetil
 - A and B only
- Match the topical retinoid to its appropriate nuclear receptors.

A. Tretinoin	i. RAR- β and RAR- γ equally; weakly to RAR- α
B. Alitretinoin	ii. All subtypes of RXR equally
C. Adapalene	iii. All subtypes of RAR and RXR
D. Tazarotene	iv. RAR- β > RAR- γ > RAR- α
E. Bexarotene	v. All subtypes of RAR equally

6. Match the following antibiotic to its appropriate side effect.

A. Minocycline	i. Thrombocytopenia
B. Erythromycin estolate	ii. Linear IgA bullous dermatosis
C. Linezolid	iii. Serum sickness like reaction
D. Vancomycin	iv. Osteoma cutis
E. Cefaclor	v. Cholestatic jaundice
7. All of the following metabolic abnormalities can be caused by cyclosporine EXCEPT:
 - A. Hyperkalemia
 - B. Hyperuricemia
 - C. Hypomagnesemia
 - D. Hyperlipidemia
8. Match the appropriate class of antifungal with its mechanism of action.

A. Allylamines	i. Interferes with microtubule formation
B. Azoles	ii. Inhibits glucan synthesis
C. Echinocandins	iii. Inhibits lanosterol 14- α -demethylase
D. Griseofulvin	iv. Binds to ergosterol and forms membrane pores
E. Polyenes	v. Inhibits squalene epoxidase
9. All of the following immunobiologicals are pregnancy category B EXCEPT:
 - A. Efalizumab
 - B. Adalimumab
 - C. Etanercept
 - D. Infliximab
10. In an average adult, approximately how many grams of ointment does the whole body require in a single dose?
 - A. 5–10 g
 - B. 20–30 g
 - C. 60–70 g
 - D. 100–110 g

Answers

1. A. ii; B. i; C. i; D. ii; Folate is converted to dihydrofolate by dihydropteroate synthetase, which is blocked by dapsone and sulfonamides. Dihydrofolate is then converted to tetrahydrofolate by dihydrofolate reductase, which is blocked by methotrexate and trimethoprim. Note that methotrexate competitively and irreversibly inhibits dihydrofolate reductase. Furthermore, tetrahydrofolate is used as a cofactor and acted on by thymidylate synthetase for DNA synthesis. Methotrexate also causes partial, reversible inhibition of thymidylate synthetase.
2. C. The risk of cataracts, osteoporosis, and possibly osteonecrosis are not reduced by alternate day dosing of corticosteroids. However, the risk of adrenal crisis can be reduced by alternate dosing.
3. B. ACE inhibitors, folate antagonists such as methotrexate, and xanthine oxidase inhibitors such as allopurinol can increase the risk of myelosuppression when given with azathioprine. Beta blockers are not associated with this risk.
4. D. Both cyclophosphamide and chlorambucil can cause azoospermia and amenorrhea. It can occur after prolonged therapy and may be irreversible with cyclophosphamide. Mycophenolate mofetil is not associated with reproductive side effects and most commonly causes dose dependent gastrointestinal side effects.
5. A. v; B. iii; C. i; D. iv; E. ii. Tretinoin binds to all subtypes of RAR equally. Alitretinoin binds to all subtypes of RAR and RXR, although with slightly more affinity to RAR. Adapalene binds to RAR- β and RAR- γ equally; weakly to RAR- α . Tazarotene binds to RAR- β > RAR- γ > RAR- α . Bexarotene binds to all subtypes of RXR equally. Note that RAR- γ is the predominant nuclear receptor in the epidermis.
6. A. iv; B. v; C. i; D. ii; E. iii. Minocycline can cause osteoma cutis. The estolate form of erythromycin can cause cholestatic jaundice. Linezolid can cause reversible thrombocytopenia. Vancomycin can cause linear IgA disease. Cefaclor can cause serum sickness like reaction.
7. C. Cyclosporine can cause hypomagnesemia. Besides metabolic abnormalities, cyclosporine can also cause hypertension in approximately one quarter of patients and blood pressure should be checked on every visit.
8. A. v; B. iii; C. ii; D. i; E. iv. In the fungal cell membrane synthesis pathway, squalene is converted to lanosterol by squalene epoxidase, which is blocked by allylamines. Lanosterol is converted to 14- α demethyl lanosterol by cytochrome p-450 dependent 14- α demethylase. This enzyme is blocked by the azoles. The end product, ergosterol, cannot be synthesized. The echinocandins (capsosfungin) inhibits glucan synthesis, an essential polysaccharide of the fungal cell wall. The polyenes (amphotericin) binds to ergosterol and forms membrane pores altering permeability to ions. Griseofulvin interferes with microtubule formation and causes metaphase arrest.

9. A. Efalizumab is pregnancy category C. Adalimumab, etanercept, infliximab, and alefacept are all pregnancy category B.
10. B. The whole body of an average adult requires 20–30 g of ointment per single dose. Face or neck requires 1 g. Each side of trunk requires 3 g. Each arm requires 1½ g. Each hand requires ½ g. Each leg requires 3 g. Each foot requires 1 g.

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SURGERY AND ANATOMY

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ANATOMIC REVIEW OF ARTERIES AND VEINS AND LYMPHATICS

Arteries of the Head and Neck (Fig. 25-1, Table 25-1)

- Blood supply to the head and neck
 - The internal carotid artery (ICA)
 - External carotid artery (ECA) and their branches
- Intimate anastomoses between ICA and ECA in the region of the upper central face (nose, glabella, periorbital, and forehead)
- These connections are important clinically in that:
 - Infections in this area may extend intracranially via ICA
 - Steroid injections in the periorbital skin may embolize to the retinal artery and cause blindness
- Named arteries give rise to unnamed branches and perforators that nourish overlying muscles, fascia, subcutaneous fat, and skin
 - *Septocutaneous arteries*: travel through septa to skin
 - *Musculocutaneous arteries*: perforate muscles to skin
 - *Subdermal plexus arteries*: at the junction of the subcutaneous fat and the deep reticular dermis
 - Arise from septocutaneous and musculocutaneous arteries
 - Main blood supply to the skin
 - Undermine at least below midfat to preserve the subdermal plexus as immediate subdermal undermining may compromise the subdermal plexus

Venous System of the Lower Extremities (Fig. 25-2, Table 25-2)

- Consists of the superficial (above muscular fascia) and deep (below muscular fascia) venous system
- The superficial and deep systems are connected via perforator veins

- Flow is unidirectional
 - Superficial veins drain into the deep veins via the perforators
 - Deep veins merge to form the common femoral vein
 - Venous valves permit only one-way flow (upward), when competent
 - Greatest density in the calf and progressively fewer valves in the thigh
- Calf muscles act as a muscular pump to drain venous blood
 - Venous blood is moved only during muscle contraction
 - Lying still or standing still does not drain the venous system

Lymphatics

LYMPH GLANDS OF THE HEAD AND NECK

- See Figure 25-3

LYMPH GLANDS OF THE UPPER EXTREMITY

- Divided into two sets: superficial and deep
 - Superficial lymph glands: few and of small size
 - Deep lymph glands: chiefly grouped in the axilla

LYMPHATICS OF THE LOWER EXTREMITY

- *Anterior tibial gland*: small and inconstant
- *Popliteal glands*: small in size and some six or seven in number; imbedded in the fat
- *Inguinal glands*: situated at the upper part of the femoral triangle

ANATOMIC REVIEW OF MUSCLES

See Tables 25-3 and 25-4.

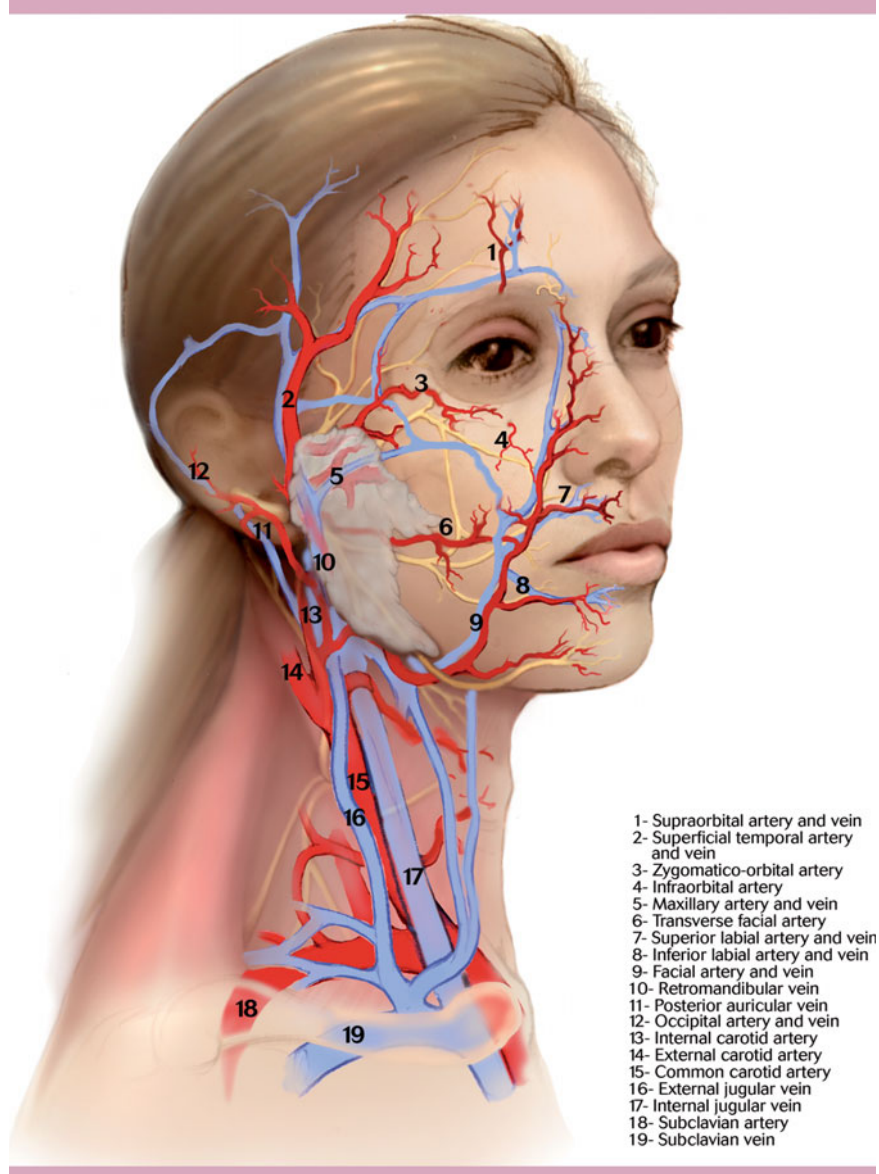


FIGURE 25-1 Arteries of the head and neck.

ANATOMIC REVIEW OF NERVES

Nerve Blocks: General Considerations

- Aspirate before injecting
 - Use a 30-gauge needle with a 60-degree beveled point
 - If pain/dysesthesia is elicited during insertion or injection, withdraw the needle slightly to avoid injuring the nerve itself
 - Do not inject the nerve directly; goal is to bathe the perineural space with local anesthetic
 - Wait at least 10 to 20 minutes for effective anesthesia
 - Most importantly: know your anatomy

Innervation of the Head and Neck (Tables 25-5, 25-6, and 25-7; Figs. 25-5 and 25-6)

- *Facial nerve (CN VII)*
 - Emerges from cranium through the stylomastoid foramen and runs in the deep body of the parotid in the lateral cheek/jaw
 - *Sensory* (minor role): sensation to the external auditory meatus along with auriculotemporal and vagus nerves
 - *Motor* (major function): five branches that innervate the muscles of facial expression:
 - Temporal
 - Zygomatic
 - Buccal

TABLE 25-1 Branches of the Carotid Artery

Internal Carotid Artery Branches	External Carotid Artery Branches
<p>Supplies structures inside the skull, except for central facial arteries that nourish the periorbital skin, forehead, glabella, and nose:</p> <ul style="list-style-type: none">• Supraorbital• Supratrochlear• Infratrochlear• Dorsal nasal• External nasal arteries	<ul style="list-style-type: none">• Superficial temporal• Maxillary<ul style="list-style-type: none">– Anterior tympanic– Middle meningeal– Inferior alveolar– Accessory meningeal– Masseteric– Pterygoid– Deep temporal– Buccal– Sphenopalatine– Descending palatine– Infraorbital– Posterior superior alveolar– Middle superior alveolar– Pharyngeal– Anterior superior alveolar– Artery of the pterygoid canal• Posterior auricular• Occipital• Facial• Lingual• Ascending pharyngeal• Superior thyroid

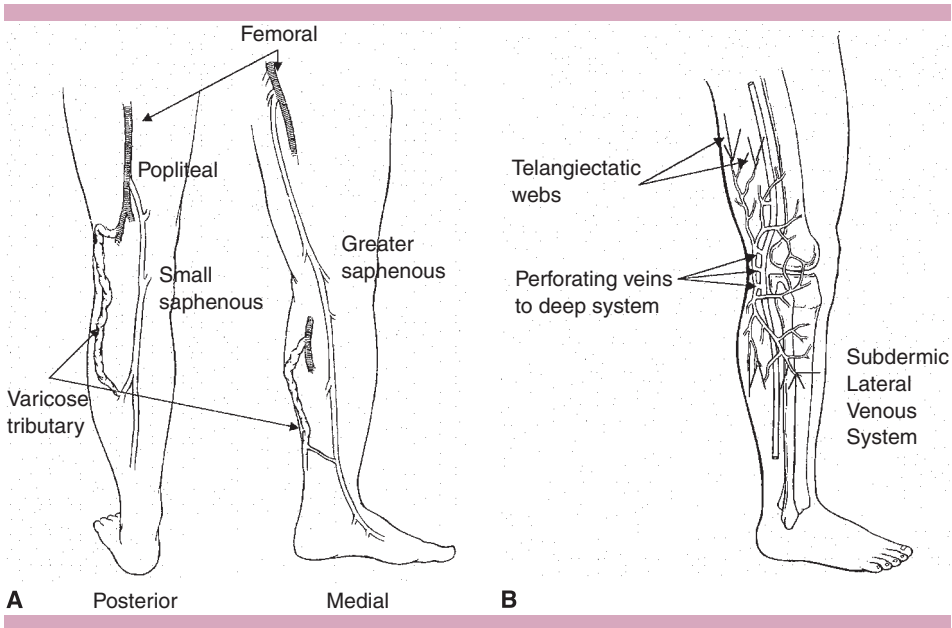


FIGURE 25-2 Venous system of the lower extremities. (Reproduced with permission from Freedberg IM et al: Fitzpatrick’s Dermatology in General Medicine, 6th ed. New York: McGraw-Hill; 2003.)

TABLE 25-2 Leg Veins

	Superficial Leg Veins	Deep Leg Veins
Location	<p>Veins lie above the deep muscular fascia and drain into the deep venous system</p> <p>There are three major networks in the superficial venous system</p> <p>Great saphenous vein (GSV)</p> <ul style="list-style-type: none"> • Originates from the dorsal arch veins of the foot, runs anterior to medial malleolus, up medial calf, knee, and inner thigh, and empties into the common femoral vein via the saphenofemoral junction (SFJ) • The longest superficial vein of the lower leg • Most common cause of superficial venous insufficiency <p>Small saphenous vein (SSV)</p> <ul style="list-style-type: none"> • Runs behind the lateral malleolus, up the posterior calf, and empties into the popliteal vein (where it empties may vary with individuals) within or near the popliteal fossa • Drains skin and superficial fascia of the lateral and posterior side of the foot and leg <p>Lateral venous system (LVS)</p> <ul style="list-style-type: none"> • Lateral venous system: series of veins on the lateral thigh that drain this area 	<p>Veins lie below the deep muscular fascia</p> <p>Tibial veins: anterior and posterior (aTV, pTV)</p> <ul style="list-style-type: none"> • Drain into popliteal vein <p>Popliteal vein (PV)</p> <ul style="list-style-type: none"> • Drains into superficial femoral vein <p>Femoral vein (FV)</p> <ul style="list-style-type: none"> • Joins with deep femoral vein in thigh to form common femoral vein • This is a deep vein despite its name <p>Deep femoral vein (DFV)</p> <p>Common femoral vein (CFV)</p> <ul style="list-style-type: none"> • At the groin/upper thigh, this is the site of drainage for multiple veins: <ul style="list-style-type: none"> – GSV – Circumflex-iliac – External pudendal – Epigastric
Comment	<ul style="list-style-type: none"> • Anterolateral thigh vein: drains the lateral and anterior thigh; empties into the GSV; lateral segment is part of the lateral venous system • Venous thromboses in a superficial vein do not have to be treated with anticoagulation unless the thrombus is progressive or near the junction with a deep vein (proximal thrombus) 	

- Marginal mandibular
- Cervical
- *Trigeminal nerve (CN V) (Table 25-6)*
- *Cervical plexus (Table 25-7)*
 - Facial nerve blocks
 - The most common facial nerve blocks target supraorbital (V1), infraorbital (V2), and mental (V3) nerves which exit into the face through foramina of the same names
 - These three nerves line up vertically at the midpupillary line, which is 2.5 cm from the facial midline (Fig. 25-6)
 - Intraoral approach to infraorbital and mental nerve is preferred to reduce patient discomfort, which is greater with transcutaneous injections
- Supraorbital nerve block
 - Supraorbital and supratrochlear nerves innervate the frontal part of scalp and forehead

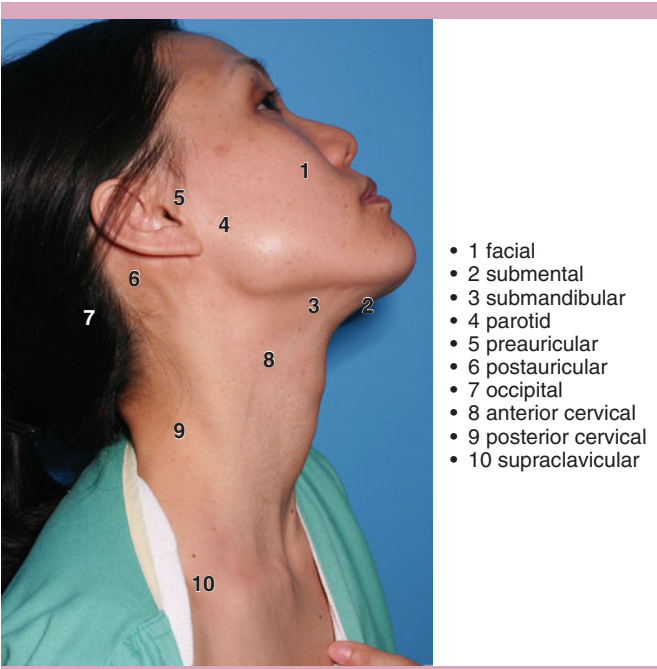


FIGURE 25-3 Lymph nodes of the head and neck.

- Supraorbital foramen/notch may or may not be palpable. Use the midpupillary line as a guide to the supraorbital nerve
- With patient in slight reverse Trendelenburg, stand behind the patient’s head. This position will afford better access to the superior orbital rim and prevent the patient from seeing the needle approach
- Raise a cutaneous wheal of anesthesia over the superior orbital rim in the midpupillary line. Insert the needle down to the rim until resistance is felt. Aspirate to ensure no blood return, and

- then inject 1 to 2 mL and massage the site to spread the anesthetic near the nerve
- If no resistance is felt after inserting the needle 1 cm, then you are likely below the orbital rim or in the foramen itself. Withdraw the needle, and then insert it again, but redirect it to be above the rim
- To extend the block medially or laterally, a bleb of anesthesia may be injected along the superior orbital rim medially and laterally from the supraorbital starting point
- Infraorbital nerve block
 - Infraorbital nerve innervates the lower eyelid, medial aspect of the cheek, upper lip, and lateral portion of the nose
 - Intraoral (mucosal) approach is preferred
 - Use a 1-inch 30-gauge needle, and when possible, apply viscous lidocaine or EMLA cream to the gingival sulcus above the upper canines for 5 minutes prior to injection
 - Position yourself on the opposite side of the nerve to be blocked, and have the patient slightly turn his or her head toward you. For example, to block the right infraorbital nerve, stand at the patient’s left side. This permits better access to the medially oriented foramen and causes less flexion of the injecting wrist
 - Place the third or fourth finger of the noninjecting hand over the infraorbital foramen (1 cm below the palpable infraorbital margin), and peel back the ipsilateral upper lip with the index finger and thumb of the same hand (use a gauze to lift up the lip to avoid slipping)
 - Inject a bleb of anesthesia at the gingival-labial sulcus above the apex of the canine fossa. Insert and aim the needle toward the foramen, or just

TABLE 25-3 Embryology

Group	Muscles	Derived From	Comment
Muscles of mastication	Temporalis, masseter, medial pterygoid, lateral pterygoid	First branchial arch mesoderm	Trigeminal nerve (CN V)
Muscles of facial expression	See Fig. 25-4 and Table 25-4	Second branchial arch mesoderm	Facial nerve (CN VII)
Lower face muscles	Risorius, platysma, depressor anguli oris	Embryonic platysma	Tend to not have bony insertions or origins
Middle and upper face muscles	Muscles of the forehead, scalp, periorbital, upper mouth	Embryonic sphincter colli profundus muscle	May have bony insertions

TABLE 25-4 Muscles of Facial Expression With Innervations (Fig. 25-4)

Muscle	Action	Rhytids	Branch of Facial Nerve
Upper Face Muscles			
Scalp			
– Occipitalis	Moves scalp posteriorly		Postauricular
– Frontalis	Raises eyebrows Wrinkles forehead	Horizontal forehead lines	Temporal
Periorbital			
– Corrugator supercolli	Pulls eyebrows medially	Glabellar lines	Temporal
– Orbicularis oculi	Closes and squeezes eyelids shut	Crow's feet	Temporal Zygomatic
Nose			
– Procerus	Pulls skin over glabella inferiorly Wrinkles nose upwards		Temporal Zygomatic
– Zygomaticus major and minor	Elevates corner of mouth		Zygomatic Buccal
– Nasalis	Dilates nares	Bunny lines	Buccal
– Depressor septi nasi	Pulls columella inferiorly		Buccal
Mouth-Lip Elevators			
– Levator labii superioris	Elevates upper lip		Buccal
– Levator labii superioris alaeque nasi	Lifts upper lip Dilates nares		Buccal
– Levator anguli oris	Elevates corner of mouth		Buccal
– Risorius	Pulls corner of mouth laterally		Buccal
Mouth-Lip Depressors			
– Buccinator	Flattens cheek Whistle, blow		Buccal
– Depressor anguli oris	Depresses corner of mouth (Marionette lines)		Buccal Marginal mandibular
– Depressor labii inferioris	Depresses lower lip		Marginal mandibular
– Mentalis	Protrudes lower lip	Mental crease	Marginal mandibular
– Orbicularis oris	Closes mouth Purses lips Pucker Protrudes lip	Vertical lip lines	Buccal Marginal mandibular
– Platysma	Pulls corner of mouth inferiorly Webs, tenses neck	Horizontal neck lines	Cervical

TABLE 25-5 Motor Nerves to the Face

Nerve	Innervates
Mandibular branch of trigeminal (CN V3)	Muscles of mastication
Facial nerve (CN 7)	Muscles of facial expression
Oculomotor (CN 3)	Levator palpebrae superioris (LPS)
Sympathetic innervation	Superior palpebral muscle of Müller (involuntary elevates upper eyelid in flight or fight situations)

TABLE 25-6 Three Branches of the Trigeminal Nerve (CN V) (Provide Sensation to the Head) (Fig. 25-5)

CNV Branch	Ophthalmic Nerve (V1 Sensory)	Maxillary Nerve (V2 Sensory)	Mandibular Nerve (V3 Sensory)
Location	Travels through superior orbital fissure (SOF) and passes through orbit Divides into three branches	Leaves the skull through the foramen rotundum Divides into four branches	Exits the cranium through the foramen ovale. Divides into five branches
Branches	Frontal nerve <ul style="list-style-type: none">• Supraorbital nerve• Supratrochlear nerve Nasociliary nerve <ul style="list-style-type: none">• Infratrochlear nerve• External nasal branch of anterior ethmoid Lacrimal nerve	Zygomaticotemporal Zygomaticofacial Infraorbital Nasopalatine <ul style="list-style-type: none">• superior alveolar and palatine nerves (sensation to upper teeth, gingival, palate, nasal mucosa)	Buccal nerve Lingual nerve Mental nerve Inferior alveolar nerve Auriculotemporal nerve
Innervates	Forehead Scalp	Side of the nose Lower eyelid Upper lip	Mucous membranes of the mouth and cheek Anterior two-thirds of the tongue Lower teeth Skin of the lower jaw Side of the head and scalp Meninges of the anterior and middle cranial fossae

below the overlying finger. Stop when resistance or bone is felt

- Aspirate and confirm that no blood returns, and then inject 2 to 3 mL of local anesthetic. If you are in the proper location, then the finger overlying the infraorbital foramen should feel a bleb of anesthesia

rise from underneath. Withdraw slightly, and inject another 1 to 2 mL laterally on each side of the infraorbital foramen. Massage the injected site

- Mental nerve block (Fig. 25-7)
 - Mental nerve innervates the lower lip and chin
 - Intraoral (mucosal) approach is preferred

IV. Muscles of facial expression and neck muscles

- 1- Galea aponeurotica
- 2- Frontalis (frontal belly) of epicranii muscle
- 3- Corrugator supercilii muscle
- 4- Procerus muscle
- 5- Orbicularis oculi muscle:
 - a.- Orbital part
 - b.- Palpebral part
- 6- Zygomaticus major muscle
- 7- Zygomaticus minor muscle
- 8- Levator labii superioris muscle
- 9- Levator labii superioris alaeque nasi muscle
- 10- Nasalis muscle
- 11- Risorius muscle
- 12- Modiolus
- 13- Masseter muscle
- 14- Depressor anguli oris muscle
- 15- Depressor labii inferioris muscle
- 16- Mentalis muscle
- 17- Orbicularis oris
- 18- Depressor septi nasi muscle
- 19- Sternocleidomastoid muscle
- 20- Platysma muscle
- 21- Trapezius muscle

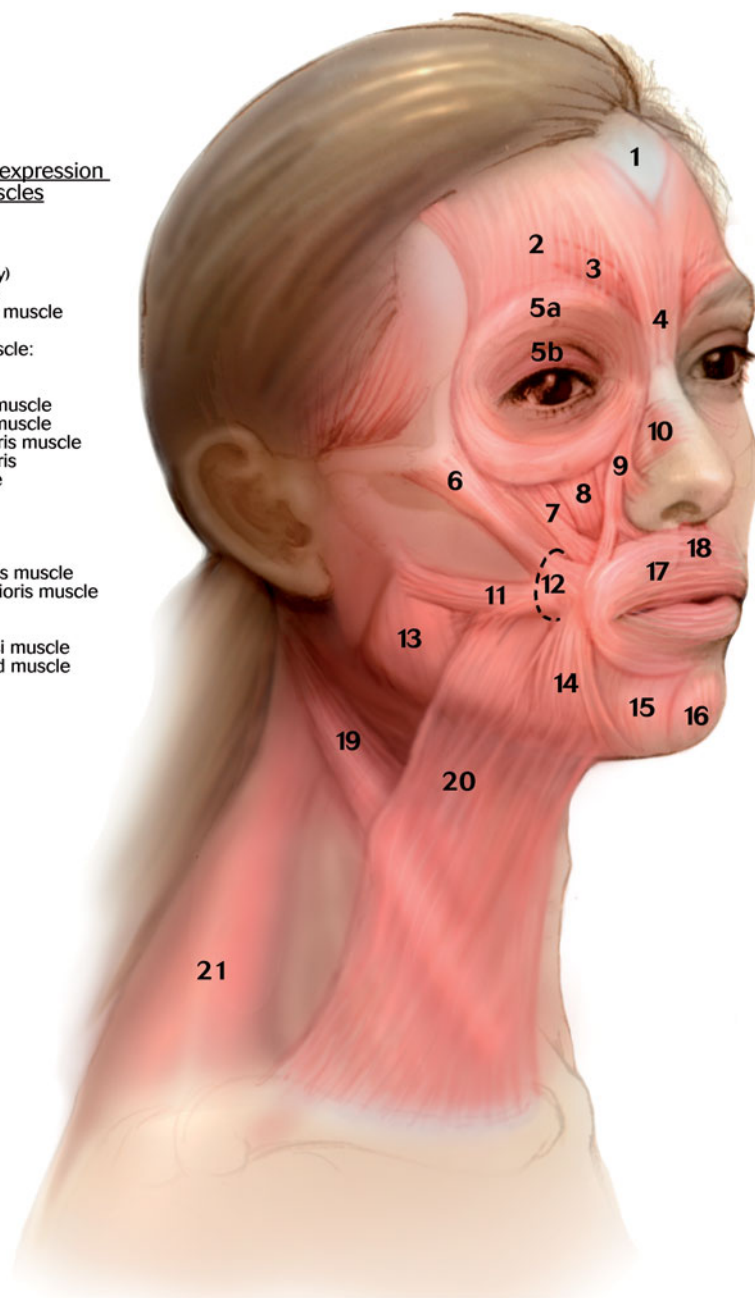


FIGURE 25-4 Muscles of facial expression.

- Use a 1-inch, 30-gauge needle, and when possible, apply viscous lidocaine or EMLA cream to the gingival-labial sulcus below the second bicuspid for 5 minutes prior to injection
- Stand behind the patient's head with the patient body in reverse Trendelenburg. Mark the mental foramen position in the midpupillary line (rarely, the foramen may be palpable (the

foramen is approximately midway between the oral commissure and the mandibular rim in the midpupillary line), and place the third or fourth finger of the noninjecting hand over this site. Peel the ipsilateral lower lip outward with the index finger and thumb of the same hand

- Inject and raise a bleb of local anesthetic at the gingival-labial sulcus below the second

TABLE 25-7 Cervical Plexus (Three Nerves) Supplies Sensation to the Neck (See Fig. 25-6)

Nerve	Innervation
Lesser occipital	Sensation to posterior neck, scalp, occiput, and upper posterior ear
Greater auricular	Sensation to earlobe and posterior auricle
Transverse cervical	Sensation to anterior neck

All exit in proximity at the posterior border of the sternocleidomastoid muscle in a region called Erb's point (discussed in the section "Surgical Anatomy: Danger Zone").

- 1- Frontal region
- 2- Temporal region
- 3- Orbital region
- 4- Zygomatic region
- 5- Malar/infraorbital region
- 6- Glabella region
- 7- Nasal region
- 8- Nasofacial sulcus
- 9- Nasolabial fold (melolabial fold)
- 10-Parotid region
- 11- Buccal region
- 12- Oral region
 - a. upper cutaneous lip
 - b. philtrum
 - c. mucosal lip
 - d. lower cutaneous lip
 - e. mental
- 13- Submandibular triangle
- 14- Carotid triangle
- 15- Sternocleidomastoid region
- 16- Omoclavicular triangle
- 17- Lateral cervical region
- 18- Posterior cervical region

- CN V₁
- CN V₂
- CN V₃
- Anterior triangle
- Posterior triangle

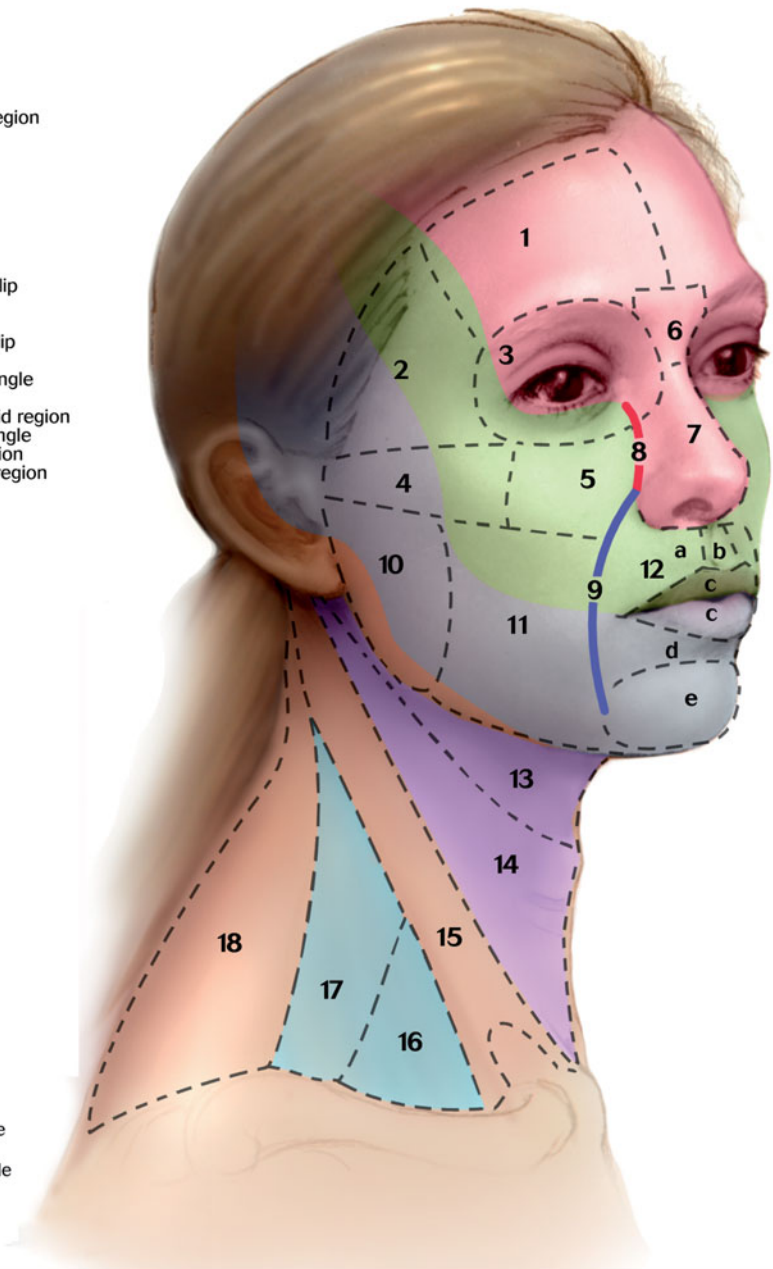


FIGURE 25-5 Facial subunits and sensory innervations: (pink) ophthalmic (V₁), (green) maxillary (V₂), (lavender/blue) mandibular (V₃).

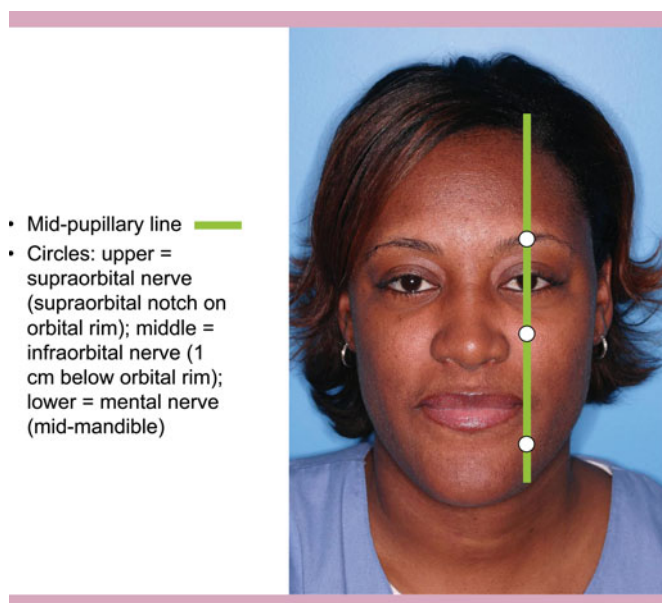


FIGURE 25-6 Mental/infraorbital nerve block landmarks: The midpupillary line is shown in green and the white circles denote the supraorbital notch on the orbital rim (top), the middle infraorbital nerve (middle), and the mental nerve (lower).

- bicuspid (second premolar). Insert and aim the needle toward the mental foramen, or below the overlying finger marking the site
- Aspirate and confirm that no blood returns, and then inject 2 to 3 mL of local anesthetic. If you are in the proper location, the finger overlying the mental foramen should feel a bleb of anesthesia rise from underneath. Withdraw slightly, and inject another 1 to 2 mL laterally on each side of the infraorbital foramen. Massage the injected site
 - Regional anesthesia for the nose
 - Sensory innervation to the nose is via the infratrochlear (V1: nasal root, middorsum, and sidewall), external nasal branch of the anterior ethmoid (V1: distal nasal dorsum and tip), infraorbital (V2: lower nasal sidewall and lateral ala), and branches of the nasopalatine (V2: columella, nasal mucosa) nerves
 - Regional anesthesia for the ear
 - For complete anesthesia of the external auricle (Fig. 25-8), five nerves must be targeted (great auricular, auriculotemporal, lesser occipital, facial, and vagus nerves). Four injection sites are required, and anesthesia is fanned peripherally in a ring-block fashion
 - *Nerves of the hand and fingers (Fig. 25-9, Table 25-8)*
 - Innervated by:

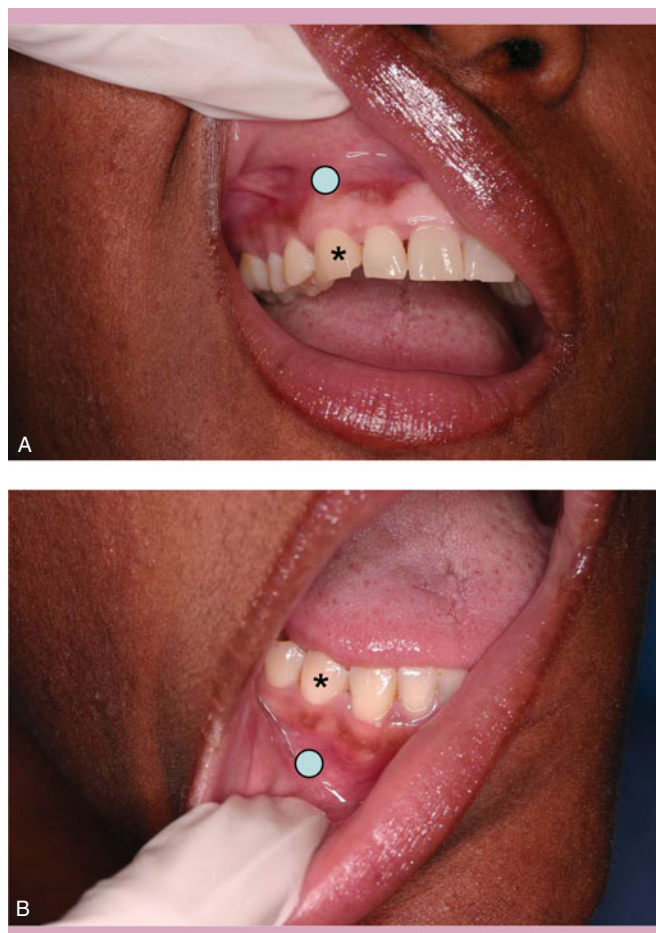
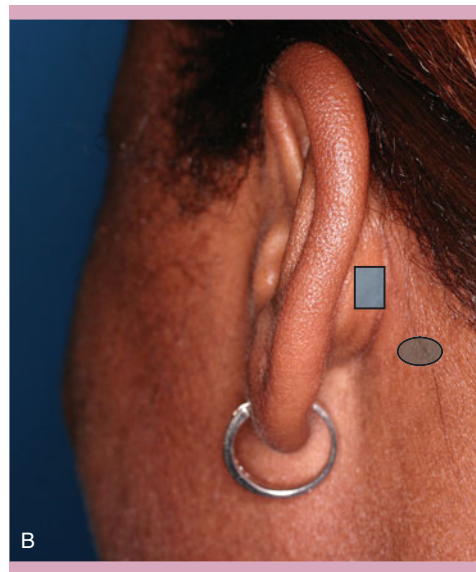
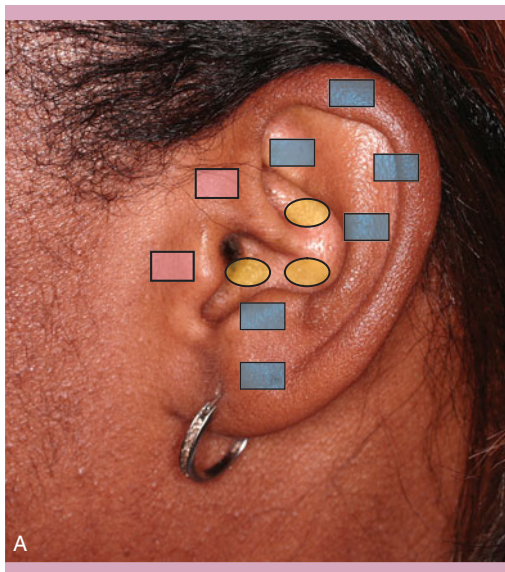


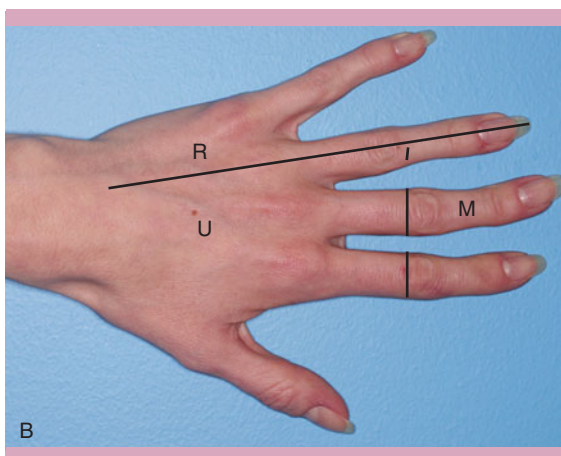
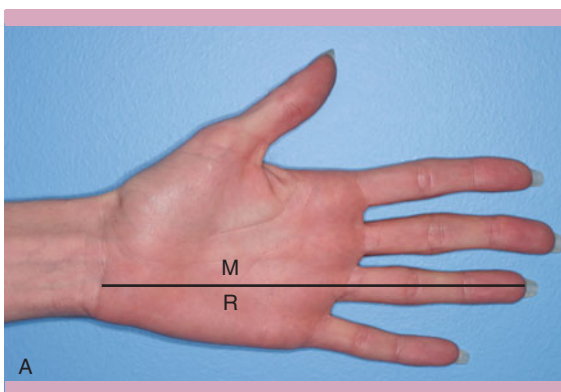
FIGURE 25-7 (A, B) Technique for mental/infraorbital nerve block: the mucosal approach in which the injection is made at the gingivolabial sulcus (blue dot) at the superior or inferior canine (*) is less painful.

- Radial nerve
- Ulnar nerve
- Median nerve
- Hand blocks
 - Median nerve block (Fig. 25-10)
 - Median nerve innervates the skin of the palmar side of the thumb, the index and middle finger, half the ring finger, and the nail bed of these fingers. The lateral part of the palm is supplied by the palmar cutaneous branch of the median nerve
 - Nerve enters the hand between the flexor carpi radialis (radial side) and palmaris longus (ulnar side) tendons beneath the flexor retinaculum
 - Both tendons are identified by asking the patient to oppose the thumb and the fifth digit



- Great auricular nerve (C2, C3)
- Auriculotemporal nerve (CNVII)
- CNVII, IX, X
- Lesser occipital (C2, C3)

FIGURE 25-8 (A, B) Sensory innervation of the ear.



- Sensory Innervation:
- Palmar surface (Top)
- Dorsal surface (Below)

FIGURE 25-9 (A, B) Innervation of the hand: R = radial nerve, M = median nerve, U = ulnar nerve.

- Needle is angled at 45 degrees and enters between the tendons at the level of the proximal wrist crease
- Inject 2 to 5 mL local anesthetic
- If the patient has congenital absence of the palmaris longus muscle, the injection can be made on the medial aspect (toward the ulna) of the flexor carpi radialis tendon
- As the needle passes through the flexor retinaculum, a loss of resistance is felt, marking the point at which the injection should be made
- If paresthesias are elicited, the needle should be withdrawn slightly (i.e., approximately 2 mm) to avoid nerve damage or intraneural injection
- Digital nerve block (Fig. 25-11)
 - On the dorsal surface of the fingers, the digital nerves are branches of the radial and ulnar nerves
 - On the ventral or palmar surface of the fingers, the digital nerves are branches of the median and ulnar nerves
 - The digital nerves that supply the toes are branches of the peroneal nerve on the dorsal surface, whereas the tibial nerve innervates the ventral or plantar surface of the toes
 - Avoid circumferential injections, which may lead to digital ischemia
 - Limit injection volumes to 3 mL total
 - Epinephrine may be used cautiously in digital blocks (see epinephrine discussion in section on local anesthesia below)

TABLE 25-8 Innervation of the Hand and Fingers (Fig. 25-10)

	Radial	Ulnar	Median
Motor			
		Muscles of hypothenar eminence Ulnar two lumbricals Seven interossei Adductor pollicis muscle	Muscles of thenar eminence Radial two lumbrical muscles
Sensory			
Dorsum of hand	Skin of dorsum of thumb and 2½ digits as far as the distal interphalangeal joint	Ulnar 1½ digits and adjacent part of dorsum of hand	
Palm of hand		Ulnar nerve: sensory to skin of ulnar 1½ digits	Median nerve: sensory to skin of the palmar aspect of thumb and 2½ digits, including the skin on the dorsal aspect of the distal phalanges
Fingers	Dorsal digital nerves	Dorsal digital nerves Ventral digital nerves	Ventral digital nerves

- Block should be as far back as possible from the surgical site
- Two nerves run on each side of the fingers and toes
- These may be blocked with injections on each side of the digit
- Needle is inserted perpendicular to the digit, midway between the palmar and dorsal surfaces of the digit, 1 to 2 cm distal to the web space
- Once resistance or bone is felt, aspirate to ensure no blood return, then inject 0.5 mL
- Withdraw the needle slightly, and redirect the needle to the dorsal surface, and inject 0.5 mL
- Repeat 0.5 mL for the palmar surface
- The side, palmar, and dorsal injections all may be done through one insertion point at the side of the finger by redirecting the needle
- Web space block (Fig. 25-12)
 - Provides digital nerve block
 - Needle is inserted from the dorsal aspect of the web space and advanced until the tip tents the palmar skin
- Anesthetic is administered along the side of the digit as the needle is withdrawn
- Epinephrine may be used with caution (see epinephrine discussion above and in section local anesthesia below)
- *Sensory nerves of the leg and ankle*
- Leg and ankle innervated by branches of the femoral nerve (Table 25-9):
 - Saphenous
 - Posterior tibial
 - Sural
 - Deep peroneal
 - Superficial peroneal
- Sensory innervation to the dorsum of the foot (three nerves) (Fig. 25-13)
 - Dorsum, medial: saphenous nerve
 - Dorsum, lateral: superficial peroneal nerve
 - Between first and second toes: deep peroneal nerve
- *Sensory innervation of sole of the foot (two nerves) (Fig. 25-13)*
 - Plantar surface (majority of): posterior tibial nerve

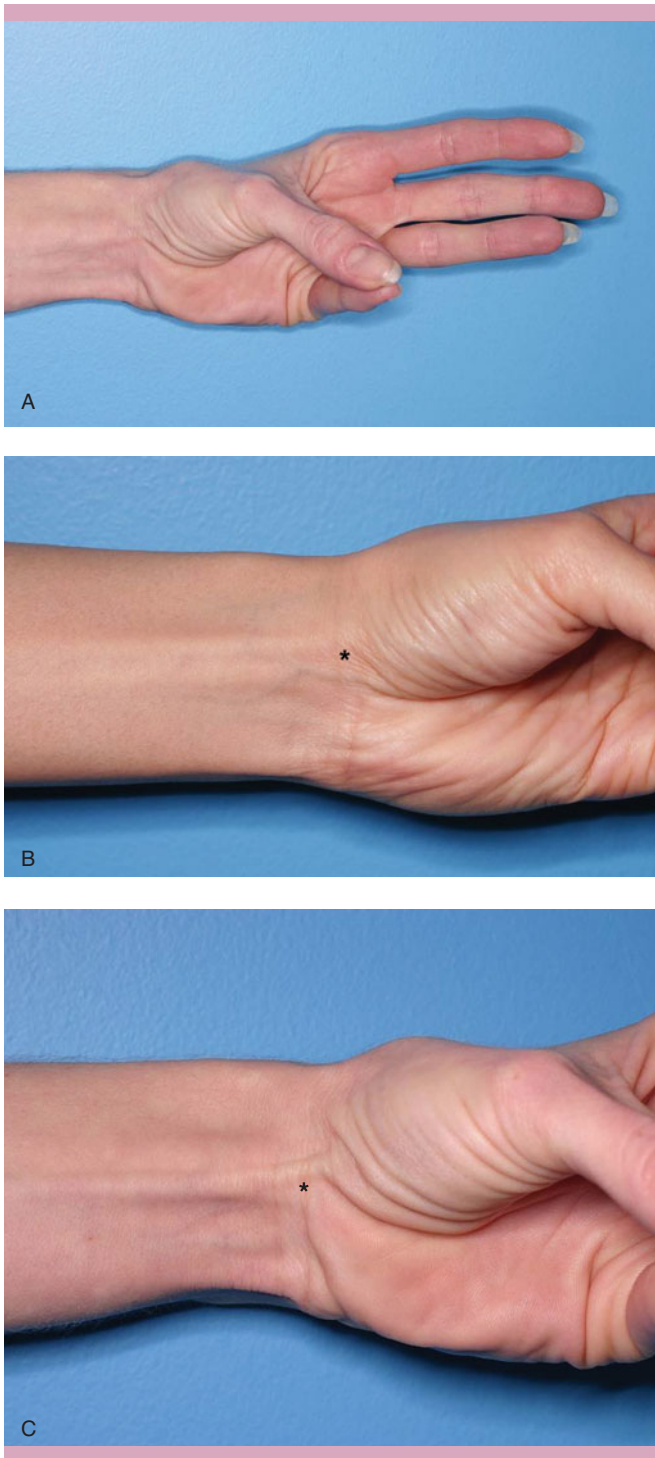


FIGURE 25-10 Technique for median nerve block of hand: to accentuate the landmarks, have the patient oppose the thumb to touch the small finger while slightly flexing the wrist (A), then inject at the wrist crease between the flexor carpi radialis and Palmaris longus (*) (B), or if the Palmaris longus is absent, inject on the ulnar side of the flexor carpi radialis (*) (C).

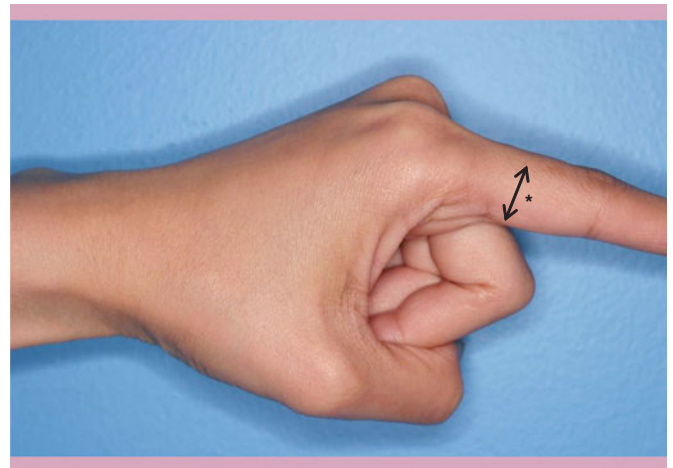


FIGURE 25-11 Digital block technique: The needle is inserted perpendicular to the digit, midway between the palmar and dorsal surfaces of the digit and 1-2 cm distal to the web space (*).



FIGURE 25-12 Web space block technique: the needle is inserted from the dorsal aspect of the web space (*) and advanced until the tip tents the palmar skin; the anesthetic is administered along the side of the digit as the needle is withdrawn.

TABLE 25-9 Femoral Nerve Branches

Branch	Comment
Saphenous nerve	Largest cutaneous branch of femoral nerve Enters foot anterior to medial malleolus Provides sensory innervation to the medial aspect of the ankle and the medial-dorsal foot up to the first metatarsal bone
Sciatic nerve	Consists of the tibial nerve and common peroneal nerves
Tibial Nerve Divides Into → Posterior Tibial Nerve + Sural Nerve	
Posterior tibial nerve	Enters foot posterior to tibial artery at medial malleolus Gives rise to two nerves that supply most of the sensation to the sole of the foot Lateral plantar nerve: lateral sole of foot Medial plantar nerve: medial sole of foot
Sural nerve	Formed by branches of the common peroneal and tibial nerves Enters the foot posterior to lateral malleolus Sensation to lateral and posterior lower third of inferior leg Sensory to small portion of lateral margin of foot and lateral side of fifth toe
Common Peroneal Nerve Divides Into → Deep Peroneal Nerve + Superficial Peroneal Nerve	
Deep peroneal nerve	Underneath flexor retinaculum anteriorly Branch of the common peroneal nerve At level of the lateral malleolus, it is bounded medially by the tendon of the extensor hallucis longus and laterally by the anterior tibial artery Skin sensation between first and second toes
Superficial peroneal nerve	Above retinaculum Skin sensation of lateral dorsum of foot and toes except for the first interdigital space (deep peroneal nerve) and lateral aspect of the foot (sural nerve)

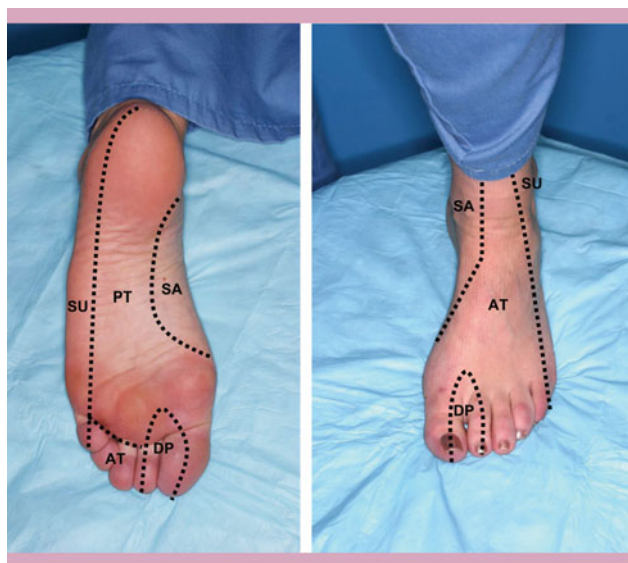


FIGURE 25-13 Innervation of the foot:
 DP = deep peroneal nerve, PT = posterior tibial nerve,
 AT = anterior tibial nerve, SU = sural nerve,
 SA = saphenous nerve.

- Lateral foot and fifth toe: sural nerve
- Nerve blocks for the foot
 - Dorsum of the foot nerve blocks: anterior ankle block
 - Superficial peroneal nerve block
 - Insert needle immediately above and anterior to the lateral malleolus
 - Inject 5 mL anesthetic subcutaneously between the anterior border of the tibia and the superior aspect of the lateral malleolus
 - Deep peroneal nerve block
 - Patient supine and the ankle in slight plantar flexion
 - Needle is inserted at the upper level of the malleoli between the tendons of the tibialis anterior and extensor hallucis longus

- Tendons can be accentuated by dorsiflexing the ankle and the great toe against resistance
- If the anterior tibial artery can be palpated, the needle should be inserted just lateral to the artery
- Needle is advanced deep to the tendons just above the periosteum, and 5 mL of 1% lidocaine is injected after aspiration
- Saphenous nerve block
 - Insert needle immediately above and anterior to the medial malleolus
 - Inject 3 to 4 mL anesthetic into the subcutaneous tissue around the great saphenous vein
- Sole of the foot nerve blocks: posterior ankle block
 - Sural nerve
 - Patient is positioned prone with the foot in slight dorsiflexion
 - Needle is inserted lateral to the Achilles tendon and 1 to 2 cm above the level of the distal tip of the lateral malleolus
 - Needle is redirected in a fan-shaped pattern from side to side as anesthetic is infiltrated
 - Posterior tibial nerve
 - Patient is positioned prone with the foot in slight dorsiflexion. Feel for the posterior tibial artery pulsation (the nerve is just behind the artery)
 - Needle is inserted midway between the medial malleolus anteriorly and the Achilles tendon posteriorly. Raise a wheal at this site, and advance the needle toward the posterior tibial artery
 - Tibial nerve lies under the dense flexor retinaculum; advance the needle until a slight give is felt as the needle penetrates the retinaculum
 - Aspirate and confirm no blood return, and inject 5 mL of 1% lidocaine. Another 5 mL is injected as the needle is withdrawn
- the three danger zones in the head and neck for motor nerve injury (Table 25-10)
- Facial layers (from most superficial to deepest) (Tables 25-11 and 25-12)
 - Epidermis (most superficial)
 - Dermis
 - Subcutaneous fat
 - SMAS
 - Muscle
 - Deep fat (variable)
 - Periosteum
 - Bone (deepest)
 - Other branches of the facial nerve: zygomatic, buccal
 - Rarely injured because they are well protected by a well-defined layer of SMAS and muscle
 - Injury to these nerves usually does not cause permanent injury because they have multiple rami and cross-innervate muscles
 - Nerves medial to a line connecting the lateral canthus to the oral commissure are usually well arborized, and permanent injury is rare medial to this line
- Undermining
 - Done to separate vertical and lateral fibrous/fascial attachments that restrict tissue mobility
 - Increases tissue mobility, decreases wound edge tension, and facilitates wound closure, thereby enhancing postoperative cosmesis
 - Undermining should always be above SMAS and muscle with few exceptions:
 - Forehead: below the frontalis muscle, between the two superior temporal lines laterally
 - Nose: below the nasalis muscle
 - Disadvantages:
 - Too deep: may injure vital structures (i.e., motor nerves or deep arteries)
 - Too superficial: may compromise tissue viability by thinning the vascular pedicle excessively

SURGICAL ANATOMY: DANGER ZONES

- The greatest danger is injury to a major motor nerve, especially at its proximal trunk, because permanent paralysis or weakness may result, causing facial asymmetry and atrophy
- All motor nerves and major vessels lie below the superficial musculoaponeurotic system (SMAS) plane and muscle
 - Staying above the SMAS (when defined) or muscle (when the SMAS is ill-defined) is always safe to avoid motor nerve injury
 - The SMAS-muscle plane, however, is thin or difficult to identify in three areas, which then are

ANATOMIC REVIEW OF HEAD AND NECK

- Superficial musculoaponeurotic System (SMAS) (Fig. 25-15)
 - A fascial envelope that encircles the muscles of facial expression in a broad plane across the face via fibrous septa that extends and inserts into the dermis above
 - It also serves as a protective anatomic plane: all major motor and sensory nerve trunks and named vessels are deep (below) to the SMAS

TABLE 25-10 Danger Zones

Nerve	Danger Zone	Innervates	Injury
CNVII Temporal branch (Motor)	<p>Temporal fossa</p> <p>Superior border: superior temporal line (line palpable from the frontal-temporal hairline to the lateral eyebrow)</p> <p>Inferior border: zygomatic arch</p> <p>Medial border: lateral orbital rim</p> <p>Posterior border: superficial temporal artery and temporal hairline</p> <p>Most vulnerable as it exits the superior parotid and crosses the zygomatic arch</p> <p>Next most vulnerable location: as it travels across the temporal fossa (temple) toward the lateral forehead.</p> <p>Nerve is protected medial to the superior temporal line because it now lies underneath the frontalis muscle</p>	Frontalis	<p>Drooping of affected eyebrow</p> <p>Flattening of the ipsilateral forehead</p>
CNVII Marginal mandibular branch (Motor)	<p>Nerve is relatively superficial as it enters the face where the anterior border of the masseter muscle and mandibular rim intersect (the facial artery also enters the face here)</p> <p>At this region, the marginal mandibular is superficial to the facial artery.</p> <p>The platysma above protects both the artery and the nerve.</p> <p>Nerve becomes even more superficial as it travels obliquely up toward the corner of the mouth.</p> <p>As long as one stays above the lip depressor muscles, however, the nerve will not be injured</p> <p>There is great variation, however, in where the nerve lies relative to the mandibular rim.</p>	Lip depressors	Asymmetry of corners of mouth
CNXI Spinal accessory nerve (Motor)	<p>Posterior cervical triangle at Erb's point (see Fig. 25-14): intersection of the following lines</p> <p>Draw a horizontal line connecting the mastoid to the mandibular angle</p> <p>At the midpoint of this line, a vertical line then is drawn inferiorly to intersect with the posterior border of the sternocleidomastoid muscle (SCM).</p> <p>The nerve is located within a 2- to 4-cm radius of this point.</p> <p>Several other nerves are at risk in this anatomic location:</p> <ul style="list-style-type: none"> • spinal accessory (motor) • greater auricular (sensory) • transverse cervical (sensory) 	Trapezius muscle	<p>Shoulder drooping</p> <p>Restricted shoulder elevation and abduction</p>

TABLE 25-11 SMAS Architecture¹¹

SMAS Layer	Type 1: Distinct SMAS Layer	Type 2: Wispy or Membranous SMAS Layer
Characteristic	Meshwork of fibrous septa envelops lobules of fat cells	Meshwork of intermingled collagen and elastic fibers and muscle fibers
Region	Forehead, temple (zone 1 in Fig. 25-15) Zygomatic, infraorbital region, and lateral part of the nasolabial fold (zone 2 in Fig. 25-15)	Upper, lower lips (zone 3 in Fig. 25-15) Medial part of the nasolabial fold (zone 2 in Fig. 25-15)

TABLE 25-12 Five Zones of SMAS^{11, 12}

Zones of SMAS	Characteristics	Region	SMAS Architecture
Fronto-occipital	Galea together with frontalis and occipitalis muscles	Forehead	Type 1: distinct
Suprazygomatic	Musculoaponeurotic excursion covering the temporal aponeurosis, including the suprazygomatic periauricular muscles	Temporal and parotid	Type 1: distinct
Infrazygomatic	Musculoaponeurotic excursion covering the cheek	Cheek	Type 1: distinct
Perioral	Musculoaponeurotic excursion covering the paranasal and perioral area	Nose, perioral, upper and lower lips	Type 2: Wispy or membranous
Platysmal	Platysma and its superficial fascia	Neck	Type 1: distinct

- With few exceptions, all motor nerves innervate their respective muscles on the muscle’s underside. Therefore, staying above the SMAS and muscle will prevent motor nerve injury
 - Peripheral sensory nerves and vessels may perforate the SMAS and travel above it in a superficial plane, but the proximal roots are still sub-SMAS
 - The SMAS in the scalp and upper face and the SMAS of the lower face fuse at the zygoma
 - Anatomic extensions of the SMAS include:
 - Superficial fascia of the face and superficial temporalis fascia (also known as the temporal-parietal fascia)
 - Superficial fascia of the parotid
 - Platysma in the neck. (NOTE: Superficial fascia of the neck, however, is not SMAS. It is deep to the SMAS/platysma and represents the superficial leaflet of the deep cervical fascia)
 - Galea on the scalp and its forehead extension (below the frontalis muscle)
 - The SMAS may be plicated and imbricated (done in face lift surgery) to draw the facial skin tight, as well as, help to decrease wound tension during reconstruction
 - Cosmetic units and subunits of the face
 - Figs. 25-16, 25-17, and 25-18 illustrate anatomy of the eyelid, nose, and ear, respectively
- ELECTROSURGERY (TABLES 25-12 AND 25-13)**
- Refers to the use of electric current in surgery to produce tissue destruction

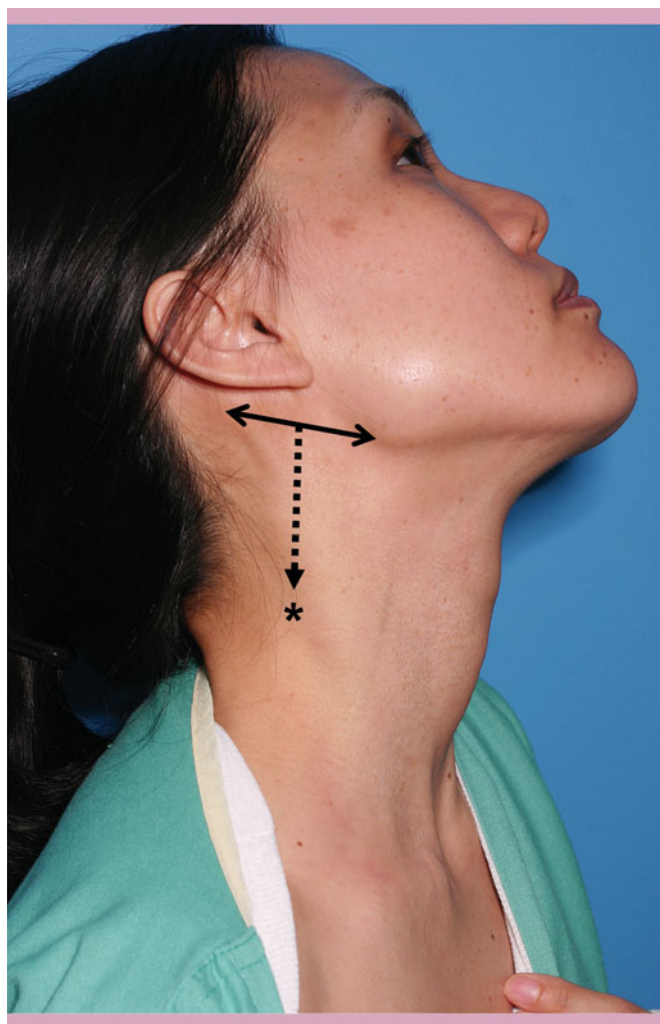


FIGURE 25-14 Erb's point (*) can be identified by drawing a line between the mastoid and jaw angle (solid arrows) and then drawing a line (dotted arrow) from the midpoint of that line to the posterior border of the sternocleidomastoid muscle. Several nerves are at risk of injury in this region, including the spinal accessory nerve, lesser occipital nerve, great auricular nerve, transverse cervical nerve, and the supraclavicular branches of the cervical plexus.

- Tissue effects from electrosurgical energy are a function of waveform, power setting, electrode size and geometry, activation time, surgical technique (orientation of electrode), and tissue impedance
- Definition of terms
 - *Electric current*: flow of electrons during a period of time, measured in amperes
 - *Circuit*: pathway for uninterrupted flow of electrons. Complete circuit must exist for electrical energy to flow

- *Complete electrical circuit*: needs three basic system components, along with the patient: a power unit, an active electrode, and a dispersive or return electrode
- *Active electrode*: i.e., handpiece
- *Dispersive, return electrode*: i.e., grounding pad
- *Resistance = impedance*: degree to which an object opposes electric current, measured in ohms
- *Voltage*: force pushing current through the resistance, measured in volts
- *Direct current (DC)*: electric current that flows in one direction (i.e., electrolysis and electrocautery)
- *Alternating current (AC)*: electrons that alternate or regularly reverse direction
- *Frequency*: measure of the number of occurrences of a repeating event per unit time, measured in hertz
- *Hertz*: number of cycles of electric current flow (one direction and back) per second
- *Radiofrequency (RF)*: an electric current occurring at high frequencies, usually > 400,000 cycles per second (Hz)
- *Electrode*: a physical device; close to or in contact with the patient, through which electrosurgical energy is received or transmitted
- *AC electrical waveforms*: may be damped or undamped to produce tissue effects of coagulation, cutting, or fulguration (desiccation)
 - *Damped*: Waves produced are initially intense and strong and then diminish rapidly. The more rapidly the sine waves return to baseline, the more damped is the current. Damped current coagulates tissue, adding to hemostasis, but causes collateral tissue damage (i.e., electrofulguration, electrodesiccation, electrocoagulation, AKA coagulation)
 - *Undamped*: Waves produced are pure sine waves. Undamped current cuts tissue without hemostatic effect (i.e., electrosection, AKA cutting)
 - *Blended current*: combined characteristics of cutting and coagulation waveforms that result in cutting with moderate hemostasis
- *Monoterminal*: delivery of current using only one treatment electrode, without a dispersive electrode (i.e., electrofulguration, electrodesiccation with hyfrecator)
- *Biterminal*: delivery of current via two electrodes, one treatment electrode and one dispersive electrode (usually at a distance from the treatment end) (i.e., electrocoagulation, electrosection). May be unipolar or bipolar
- *Unipolar*: one treatment electrode and one dispersive electrode (usually a grounding pad at distant site)

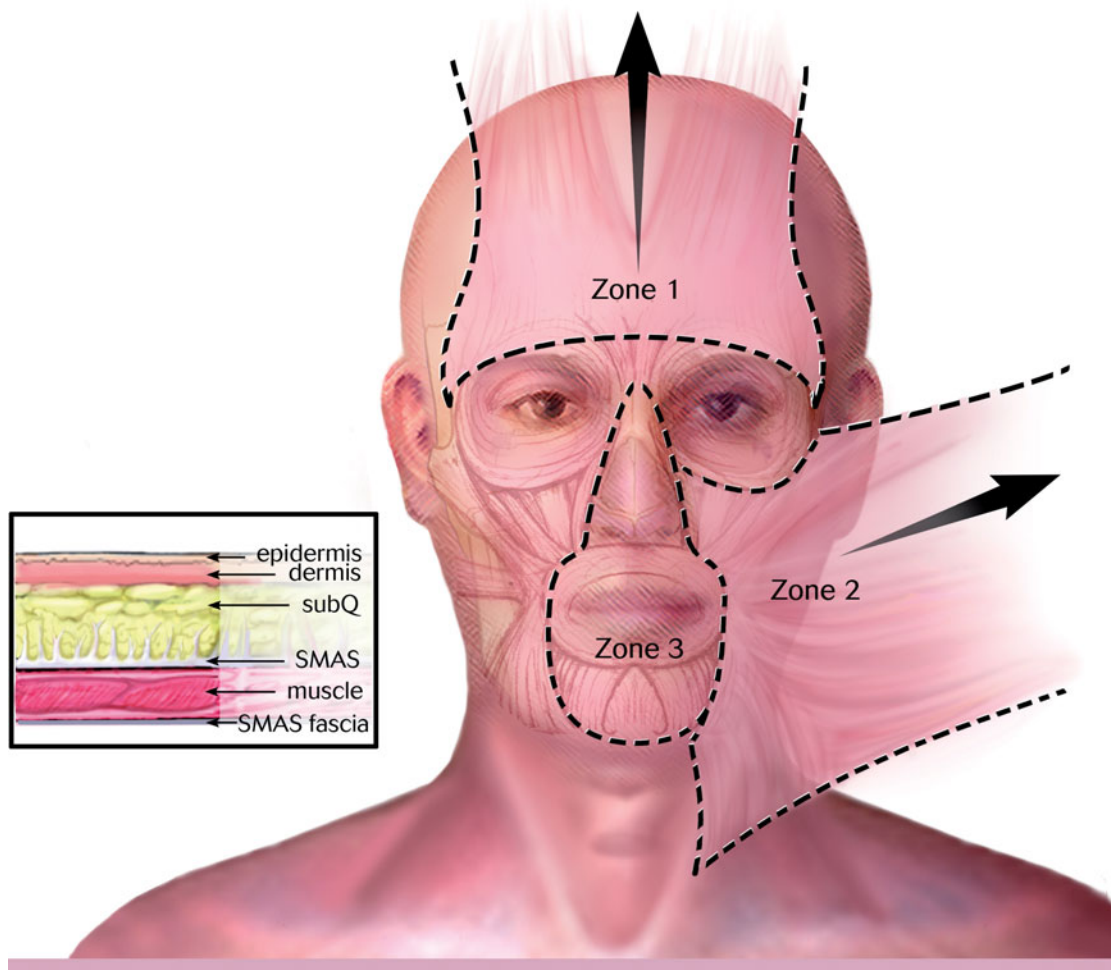
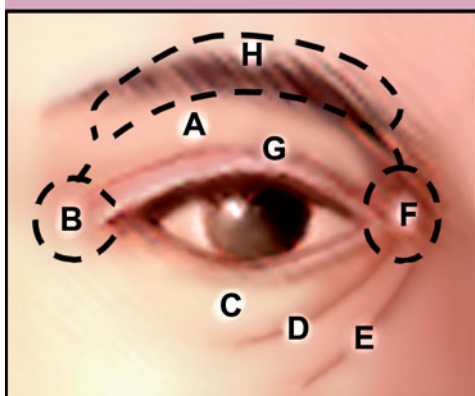


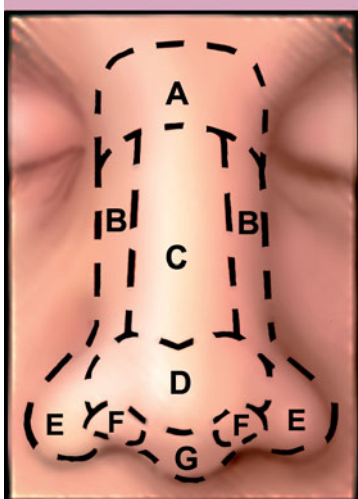
FIGURE 25-15
Superficial
musculoaponeurotic
system (SMAS).

- *Bipolar*: a forceps-like device contains both the treatment and the dispersive electrodes (dispersive pad is not required). Passage of current is restricted between these two tines, which results in substantially less tissue damage than in monopolar devices. Safest for patients with automatic implantable cardiac defibrillators (AICDs) or pacemakers
- *Electrical surgery unit (ESU)*: generates the radiofrequency current in commercial electro-surgery machines
- *Ground-referenced ESU*: the current is referenced to a ground (i.e., the electric circuit is completed through a grounded object). If there is any interruption or high impedance in the normal return path, the current will seek an alternate path, possibly causing alternate-site burns
- *Radiofrequency (RF)–isolated units*: most monopolar ESUs are now this type. The isolation transformer inside the unit isolates the therapeutic current from the ground, and therefore the therapeutic current is only returned to the ESU and is not connected to the earth ground. This arrangement eliminates the flow of energy if there is no completed pathway to the ESU
- Complications of electrosurgery
 - ESU burn: occurs when the heat produced, over time, is not dissipated safely by the size or conductivity of the patient return electrode (i.e., poor grounding pad contact). $\text{Burn} = \text{heat} \times \text{time/area}$
 - Interference with an implanted pacemaker
- Precautions in patients with an automatic implantable pacemaker and cardioverter/defibrillators (AICDs)
 - The risk of electrosurgery-induced arrhythmia is greater with an AICD than with a pacemaker



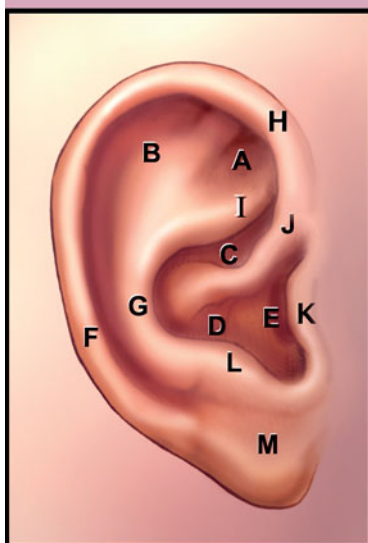
- A. Upper lid
- B. Lateral canthus
- C. Lower lid
- D. Infraorbital crease
- E. Nasojugal fold
- F. Medial canthus
- G. Superior palpebral sulcus
- H. Eyebrow

FIGURE 25-16 Eyelid anatomy.



- A. Root
- B. Lateral side wall
- C. Dorsum
- D. Tip
- E. Ala nasi
- F. Soft triangle
- G. Columella

FIGURE 25-17 Nasal anatomy.



- A. Triangular fossa
- B. Scaphoid fossa
- Concha:
 - C. Cyma
 - D. Cavum
- E. External auditory meatus
- F. Helix
- G. Antihelix
- H. Superior helix
- I. Crura of antihelix
- J. Crus of helix
- K. Tragus
- L. Antitragus
- M. Lobule

FIGURE 25-18 Ear anatomy.

TABLE 25-13 Electrosurgery

Current	Electrosurgery	Mechanism of Action	Waveform	Spark Gap Outlet	Voltage	Amperage = Current/Damage	Comments
DC	Electrolysis	<ul style="list-style-type: none"> Galvanic electrolysis works by causing salt and water in the skin around the probe to be chemically altered to produce a small amount of sodium hydroxide, or lye. If enough is produced, it can damage the cells that cause hair growth. 			Low	Low	Positive electrode = anode Negative electrode = cathode The chemical reaction is expressed like this: $\text{NaCl (salt)} + \text{H}_2\text{O (water)} + \text{direct current} = \text{NaOH (sodium hydroxide)} + \text{Cl (chlorine)} + \text{H (hydrogen)}$
DC	Electrocautery (heat)	<ul style="list-style-type: none"> Heats electrodes Rate at which heat is produced determines whether a waveform vaporizes tissue or creates a coagulum. 			Low	High	<ul style="list-style-type: none"> High heat: vaporization Low heat: coagulum
AC	Electrodesiccation (coagulation of tissue)	<ul style="list-style-type: none"> Damped waveform Treatment electrode is in direct contact with tissue No spark is generated 	Intermittent	Markedly damped	High	Low/moderate	Monoterminal
AC	Electrofulguration (coagulation of tissue)*	<ul style="list-style-type: none"> AKA noncontact surface coagulation Damped waveform 	Intermittent	Markedly damped	High	Low/moderate	Monoterminal
		<ul style="list-style-type: none"> Intermittent short bursts of high voltage produce superficial coagulation and tissue char Treatment electrode is not in contact with tissue 					

(Continued)

TABLE 25-13 (Continued)

Current	Electrosurgery	Mechanism of Action	Waveform	Spark Gap Outlet	Voltage	Amperage = Current/Damage	Comments
		<ul style="list-style-type: none"> Electric current “sparks” from the electrode tip across the air gap onto the tissue. The electrode is close enough for sparks to bridge the air gap 					
AC	Electrocoagulation (coagulation)†	<ul style="list-style-type: none"> Damped waveform that turns on and off several times per second 	Intermittent	Moderately damped	Moderate	Moderate/high	<ul style="list-style-type: none"> Biterminal Unipolar or bipolar Excellent for hemostasis of small blood vessel diameter (< 2 mm) (> 2mm may need suture ligation) Some degree of collateral tissue damage with electrocoagulation
AC	Electrosection (cut)	<ul style="list-style-type: none"> Undamped waveform concentrates energy in a small area for quick, clean cutting Causes extreme heating and vaporizing of intracellular fluid that bursts cells 	Continuous	Undamped	Low	High/high (vaporized)	<ul style="list-style-type: none"> Biterminal Bipolar

* Electrofulguration and electrodesiccation are identical in electrical properties, except that the former is noncontact, and the latter has contact with the treated tissue. Owing to direct tissue contact, charring depth may be slightly deeper in electrodesiccation than in electrofulguration

† Both electrodesiccation and electrofulguration cause superficial coagulation and have hemostatic effects. However, they are technically not electrocoagulation. Average power of coagulation current is less than that of a cutting current

- Electrosurgery current may mimic the electrical activity of the heart and stimulate the cardiac pacemaker/defibrillator, potentially causing an unnecessary shock (AICD) or an alteration of pacemaker function
- Options for patients with pacemakers or AICDs
 - Electrocautery: safe; no electric current passes into the patient
 - Bipolar (biterminal) electrocoagulation: relatively safe in patients with pacemakers and AICDs because the current is restricted between the two forcep tips
 - Unipolar electrocoagulation (biterminal): may be used cautiously in patients with pacemakers and AICDs in the following circumstances
 - ▲ Bursts of current are short (5 seconds or less)
 - ▲ Lowest effective setting is used
 - ▲ The dispersive pad/electrode is placed far away from the cardiac device such that the device is not in the path of the current flow
 - ▲ The electrosurgery is not directly over the cardiac device
 - Magnet device: placed over a cardiac pacemaker to inhibit it during the procedure. Pacemaker then must be interrogated postoperatively to ensure function
 - AICD deactivation: requires rhythm monitoring and resuscitation abilities during the procedure

CRYOSURGERY (CRYOTHERAPY)

- Defined as the application of extreme cold to destroy abnormal or diseased tissue
- Mechanism of action can be divided into three phases: (1) heat transfer, (2) cell injury, and (3) inflammation (Tables 25-14 and 25-15)
- Cryosurgery is used to treat a number of diseases and disorders
 - *Benign lesions*: verruca, xanthelasma, seborrheic keratoses, milia, venous lake, hemangiomas, keloids, lentigines or other epidermal hyperpigmentation, granuloma annulare, prurigo nodularis, myxoid cysts, condyloma
 - *Malignant lesions*: actinic keratosis, basal and squamous cell carcinomas, lentigo maligna, Kaposi's sarcoma

WOUND HEALING (TABLES 25-16 TO 25-19)

- Wound healing is the restoration of tissue continuity after injury

- Original tissue is replaced with nonspecific connective tissue, which forms a functionally inferior scar
 - 48 hours: re-epithelialization (sealing of wound)
 - 7 days: peak collagen formation
 - 3 weeks: 20% of full wound tensile strength
 - 4 months: 60% of full wound tensile strength (never exceeds 80% of full)
 - 6 to 12 months: mature scar forms
- Macrophages are the most important cells for wound healing, releasing:
 - Transforming growth factors (TGFs)
 - Cytokines
 - Interleukin-1 (IL-1)
 - Tumor necrosis factor (TNF)
 - platelet-derived growth factor (PDGF)
- Neutropenic or lymphopenic patients do not have impaired wound healing, whereas macrophage-deficient (quantity or function) patients heal poorly

ANTISEPTICS

- Infection control
 - Minor procedures (i.e., biopsies): cleanse with isopropyl alcohol and use nonsterile gloves
 - More invasive procedures (i.e., excisions with layered closure, flaps, grafts): prepare skin with either povidone-iodine or chlorhexidine scrub, followed by placement of sterile towels or drapes around the field
 - Preoperative shaving of hair has been associated with an increase in wound infections. Hairs may be trimmed but not shaved
- Antiseptic (Table 25-20)
 - Agent that kills or inhibits the growth of microorganisms on the external surfaces of the body
 - Unlike antibiotics that act selectively on a specific target, antiseptics have multiple targets and a broader spectrum of activity, which include bacteria, fungi, viruses, and protozoa

ANTIBIOTICS

- Antibiotics and surgical procedures
 - Risk of wound infection after skin surgery is small (1–2%)
 - Routine prophylactic antibiotics are usually indicated for
 - Patient populations: immunosuppressed, debilitated patients, and those with reduced blood flow to the surgical site (i.e., peripheral vascular disease, diabetes mellitus) (Tables 25-21 and 25-22)

TABLE 25-14 Cryosurgery Mechanism of Action

	Heat Transfer	Cell Freeze	Cell Injury	Inflammation										
Event	<ul style="list-style-type: none">• Cryogen (heat sink) is applied to the skin• Heat is transferred from the skin to the cryogen• Cryogen evaporates as boiling point is reached	<ul style="list-style-type: none">• Formation of ice crystals (-5 to -10°C)• Intracellular ice crystals: form with fast freeze; more destructive• Extracellular ice crystals: form with slow freeze; less tissue damage	<ul style="list-style-type: none">• Occurs during cellular thaw	<ul style="list-style-type: none">• Inflammation is the response to cell death and helps in local cell destruction										
Comment	<ul style="list-style-type: none">• Rate of heat transfer depends on the temperature difference between the skin and cryogen	<ul style="list-style-type: none">• Greatest destruction seen with rapid freeze, slow thaw• Significant vascular stasis occurs during thaw, contributing to cellular death• May cause basement membrane separation and vesicle (blister) formation	<ul style="list-style-type: none">• Cell sensitivity to cryogen damage<table><tr><td>-4 to -7°C</td><td>Melanocytes (most delicate; reason for hypopigmentation with cryotherapy)</td></tr><tr><td>-20 to -30°C</td><td>Keratinocytes</td></tr><tr><td>-30 to -35°C</td><td>Dermal fibroblasts (most resistant)</td></tr><tr><td>-50°C</td><td>Malignant tumors (core tissue temperature for optimal destruction)</td></tr><tr><td>-20 to -25°C</td><td>Benign lesions</td></tr></table>	-4 to -7°C	Melanocytes (most delicate; reason for hypopigmentation with cryotherapy)	-20 to -30°C	Keratinocytes	-30 to -35°C	Dermal fibroblasts (most resistant)	-50°C	Malignant tumors (core tissue temperature for optimal destruction)	-20 to -25°C	Benign lesions	<ul style="list-style-type: none">• Observed as erythema and edema
-4 to -7°C	Melanocytes (most delicate; reason for hypopigmentation with cryotherapy)													
-20 to -30°C	Keratinocytes													
-30 to -35°C	Dermal fibroblasts (most resistant)													
-50°C	Malignant tumors (core tissue temperature for optimal destruction)													
-20 to -25°C	Benign lesions													

TABLE 25-15 Commonly Used Cryogens and Their Temperatures

Cryogen	Boiling Point STP (°C)
Carbon dioxide (solid)	~ 78.5 (~ 109.3°F)
Nitrous oxide (liquid)	~ 89.5 (~ 129.1°F)
Liquid nitrogen	~ 195.8 (~ 320.4°F)
From Graham GF, George MN, Patel M: Cryosurgery, in Nouri K, Leal-Khoury S, eds. <i>Techniques in Dermatologic Surgery</i> . London: Mosby; 2003.	

TABLE 25-16 Categories of Wound Healing

Category	First Intention	Secondary Intention
Wound	Seen in clean, well-perfused, incised surgical wounds and casual wounds inflicted by sharp-edged objects where there is minimum destruction of tissue	When the wound is large, when there has been significant loss or destruction of tissue such that the edges cannot be apposed
Healing	Primary subtype: edges of the wound are closely apposed shortly after injury, and healing occurs without complication Delayed primary subtype: If the wound edges are not reapproximated immediately, delayed primary wound healing transpires	See Table 25-17: Phases of Wound Healing Process

TABLE 25-17 Phases of Wound Healing Process

Phase	Hemostasis	Inflammation	Granulation Re-epithelialization	Remodeling
Timing	<ul style="list-style-type: none"> Immediate 	<ul style="list-style-type: none"> First 6 to 8 hours 	<ul style="list-style-type: none"> Days 5 to 7; can last up to 4 weeks in the clean and uncontaminated wound 	<ul style="list-style-type: none"> Begins after third week; can last for years
Comment	<ul style="list-style-type: none"> Vasoconstriction Coagulation with fibrin clot 	<ul style="list-style-type: none"> Monocytes also exude from the vessels and become macrophages once in tissue Neutrophils flood the wound via TGF-β 	<ul style="list-style-type: none"> Fibroblasts have migrated into the wound, producing glycosaminoglycans (GAGs) and fibronectin Formation of new vasculature (endothelial bud formation) Reepithelialization via migration of cells from the periphery of the wound and adnexal structures 	<ul style="list-style-type: none"> Dynamic continuation of collagen synthesis and degradation Highly vascular granulation tissue undergoes a process of devascularization as it matures into less vascular scar tissue

TABLE 25-18 Growth Factors in Wound Repair

	Growth Factor	Effect
EGF	Epidermal growth factor	Reepithelialization
TGF- β	Transforming growth factor β	
KGF	Keratinocyte growth factor	Reepithelialization
HBEGF	Heparin-binding epidermal growth factor	Reepithelialization, fibroblast proliferation
PDGF	Platelet-derived growth factor	Fibroblast chemotaxis, proliferation, and contraction
IGF	Insulin-like growth factor	Fibroblast proliferation, extracellular matrix production
aFGF-1 bFGF-2	Acidic fibroblast growth factor Basic fibroblast growth factor	Fibroblast proliferation, angiogenesis
VEGF	Vascular endothelial growth factor	Angiogenesis
TGF- β	Transforming growth factor β	Fibroblast chemotaxis and contraction, extracellular matrix production, protease inhibitor production

TABLE 25-19 Macrophage Effects

Activity	Effect
Phagocytosis and killing of microorganisms	Wound decontamination
Phagocytosis of tissue debris	Wound debridement
Growth factor release	Formation of new tissue
Data from Bello Y, Falabella A, Eaglstein WH: Wound healing modalities, in Nouri K, Leal-Khouri S, eds. <i>Techniques in Dermatologic Surgery</i> . London: Mosby; 2003 and Lie J, Kirsner RS: Wound healing, in Robinson JK, Hanke WC, Sengelmann RD, et al., eds., <i>Surgery of the Skin: Procedural Dermatology</i> . London: Elsevier; 2005.	

- Anatomic sites at greater risk for infection: ears, perineum, legs, and feet
- If antibiotics are given, they must be in the bloodstream at time of surgery in order to be effective (i.e., 90 minutes before incision, but may depend on antibiotic half-life)
- Open wounds almost never become infected, whereas closed wounds with hematomas or a large amount of necrotic tissue are at increased risk for infection
- Prophylactic antiherpesvirus medications for susceptible patients undergoing lip surgery, including laser procedures
- Regimens for procedures on infected skin, skin structure or musculoskeletal tissue
- Staphylococci and (beta)-hemolytic streptococci are likely to cause infective endocarditis
- Patients with the conditions listed in Table 25-21 below who undergo a surgical procedure that involves infected skin, skin structure, or musculoskeletal tissue, should receive prophylactic antibiotics

WOUND CLOSURE

- The wound closure algorithm (Fig. 25-19) is not all inclusive

TABLE 25-20 Topical Antiseptics

	Alcohol	Chlorhexidine Gluconate	Iodine Iodophores	Hexachlorophene	Triclosan
Mode of action	Denaturation of proteins, DNA, RNA, lipids, etc.	Disruption of the microbial cell membrane with precipitation of cell contents	Iodine precipitates microorganism proteins by forming salts via direct halogenation (oxidation-substitution) Results from the combination of molecular iodine and polyvinylpyrrolidone	Disruption of the microbial cell membrane Chlorinated bisphenol antiseptic	Disruption of the microbial cell membrane Derived from phenol
Gram-positive bacteria	Excellent	Excellent	Excellent	Excellent	Good
Gram-negative bacteria	Excellent	Good	Good	Fair/Poor	Good (can use for <i>Pseudomonas</i>)
Mycobacterium tuberculosis	Good	Fair	Good	Fair	
Virus	Good	Good	Good	Fair	Unknown
Onset of action	Very rapid	Intermediate	Intermediate	Slow to intermediate	Intermediate
Residual activity	None	Excellent	Minimal	Excellent	Excellent
Toxicity/side effects	Volatile	Ototoxicity Keratitis	Absorbed through the skin; possible toxicity and irritation	Absorbed through intact skin Neurotoxic, especially in neonates	Under investigation
Precautions	Avoid open flame	Avoid contact with eyes, external auditory meatus	Molecular iodine can be very toxic for tissues; therefore, iodine is combined with a carrier, decreasing iodine availability	Avoid use on neonates, pregnant women	Avoid contact with eyes

TABLE 25-21 Cardiac Conditions Associated With the Highest Risk of Adverse Outcome From Endocarditis of Which Prophylaxis With Dental Procedures Is Reasonable

Prostatic cardiac valve or prosthetic material used for cardiac valve repair

Previous infective endocarditis

Congestive heart disease (CHD)*

- Unrepaired cyanotic CHD, including palliative shunts and conduits
- Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure[†]
- Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)

Cardiac transplantation recipients who develop cardiac valvulopathy

* Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.

[†] Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.

TABLE 25-22 Prophylactic Antibiotics Regimens

Situation	Agent	Dose	
		Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin Cefazolin or ceftriaxone	2 g IM or IV 1 g IM or IV	50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins or ampicillin – oral	Cephalexin* Clindamycin Azithromycin or clarithromycin	2 g 600 mg 500 mg	50 mg/kg 20 mg/kg 15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone clindamycin	1 g IM or IV 600 mg IM or IV	50 mg/kg IM or IV 20 mg/kg IM or IV

IM, intramuscular; IV, intravenous.

* Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage. Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

- The type of repair of a wound greatly depends on the defect location (i.e., a 1-cm defect on the nose demands greater consideration and complexity than the same sized wound on the cheek)
- *Wound defect sizes:* Small (< 1 cm), medium (1-3 cm), large (> 3 cm)
- *Location of a wound is critical*
 - Defects > 3 mm in depth will likely heal with a contour depression (unless in concave area), especially if overlying convex surfaces or sebaceous skin
 - Small, superficial defects in concave areas are ideal for second intention healing. Avoid second intention if bare bone, tendon, or neurovascular structures are exposed

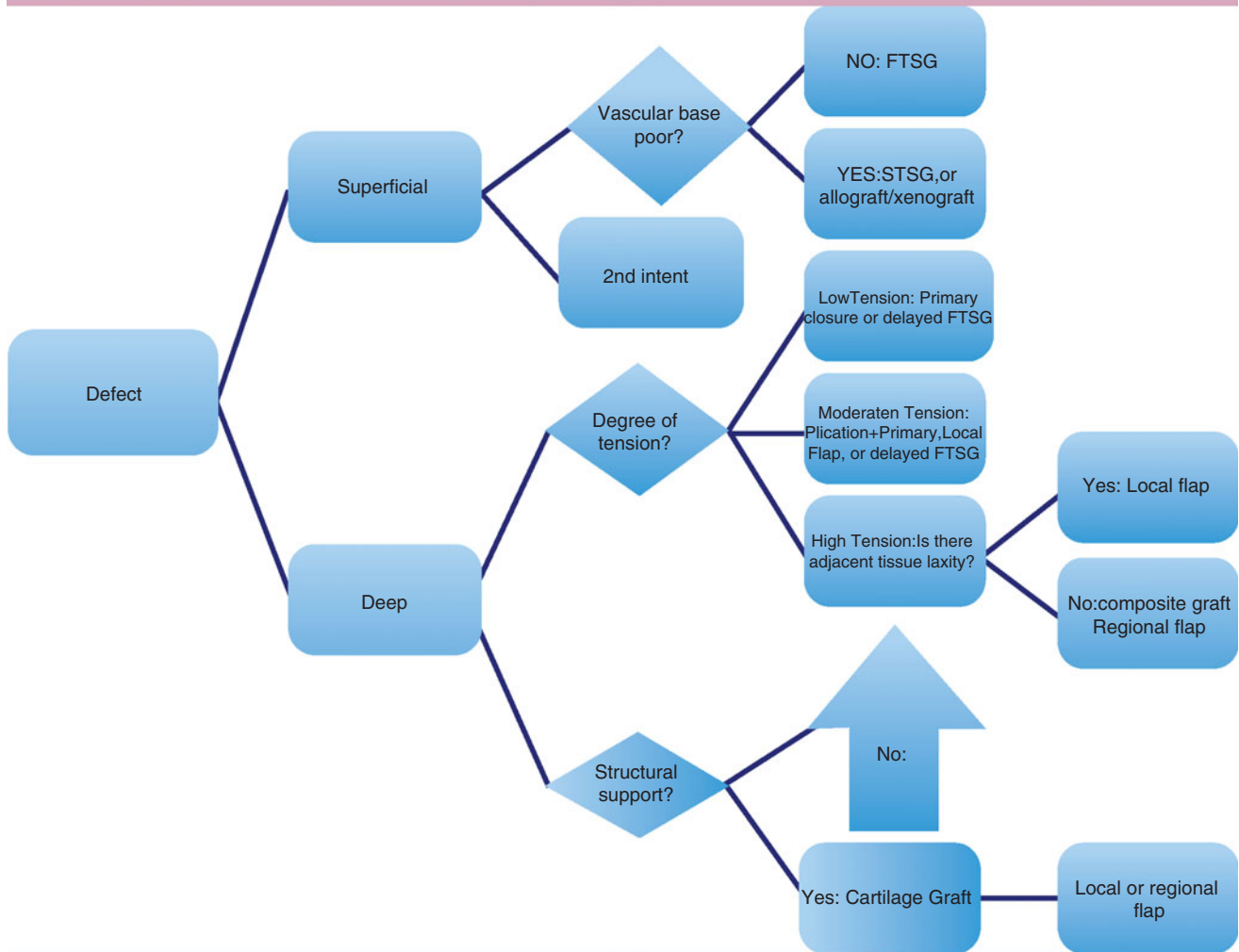


FIGURE 25-19 Wound closure algorithm.

- Large defects will also heal well if superficial. However, anticipate significant wound contraction and its impact, if any, on free margins or function
- *Full thickness skin graft (FTSG)*: consists of the epidermis and the whole thickness of the dermis, may be applied to any defect that is well vascularized
 - Superficial defects with FTSG will maintain contour
 - If deep defects are repaired with FTSG, contour depressions may result unless delayed (partial granulation to fill the depth) skin grafting is performed
- *Split thickness skin graft (STSG)*: consists of the epidermis and part of the dermis, have less metabolic demand and survive better in poorly vascularized defects. However, significant graft

contraction (with potential effect on free margins) is assured compared to FTSG

- *Composite grafts*: consists of epidermal keratinocytes seeded on a fibroblast-containing collagen matrix, work best for small deep wounds at free margins. Due to their bulk and high metabolic demand, composite grafts survive poorly if sized > 1.5 cm
- *Combination closures*: may involve flap + flap, flap + graft, or flap + 2nd intention; should be considered in wounds involving multiple subunits

FLAPS (TABLE 25-23 AND FIGS. 25-20 TO 25-32)

- Transfer of tissue (donor site) with its vascular supply into a wound defect (recipient site) for closure

TABLE 25-23 Flap Types and Characteristics

Flap Design	Advancement Flap	Rotation Flap
Examples	<p>Unilateral designs</p> <ol style="list-style-type: none"> 1. Burow's wedge advancement (Fig. 25-21) 2. Crescentic advancement (can be unilateral or bilateral (Fig. 25-22) 3. V to Y or Island pedicle (kite) (Fig. 25-23) <p>Bilateral designs</p> <ol style="list-style-type: none"> 1. H-plasty 2. A to T bilateral advancement (Fig. 25-24) <p>Interpolation subtype</p> <ol style="list-style-type: none"> 1. Retroauricular staged flap (This is a staged flap that has a linear movement. However, it may also be classified as a transposition design since it crosses over intervening island of normal skin to reach the defect.) 	<p>Rotation (Fig. 25-25)</p> <ol style="list-style-type: none"> 1. Cervicofacial rotation (Fig. 25-26) 2. Dorsal nasal rotation (Rieger, hatchet) (Fig. 25-13) 3. O to Z bilateral rotation (Fig. 25-27) 4. Innervated myocutaneous lip and cheek (Karapandzic) 5. O to T bilateral rotation 6. Comet flap <p>Transposition subtype</p> <ol style="list-style-type: none"> 1. Rhombic or Rhomboid (Limberg 60 degree, Dufourmental) 2. Webster 30 degree Note or Banner flap (Fig. 25-28) 3. Bilobe (Fig. 25-29) 4. Trilobe (Fig. 25-30) <p>Interpolation subtype</p> <ol style="list-style-type: none"> 1. Paramedian forehead flap (Fig. 25-20) 2. Lip-switch (Abbé) flap 3. Cheek-to-nose (melolabial) interpolation (Fig. 25-31)
Movement	Linear	Pivotal (movement is in an arc)
Vascular supply	Random pattern	Random pattern or Axial (paramedian forehead flap, lip-switch flap)
Flap:defect ratio	2-4:1	2-4:1 (flap:defect ratio may be greater with axial flap)
Tension	Tension is reduced and redistributed but is not redirected.	Tension is reduced, redistributed, and redirected.
Mobility	Recruits some adjacent tissue laxity laterally	Optimizes recruitment of lax donor tissue lateral and distant from the defect.
Restraint	Lateral restraint	<p>Pivotal restraint (Fig. 25-32)</p> <p>Arises from inherent tissue stiffness at the flap's pivot point and prevents the flap's tip from reaching distal margin of the operative defect. Secondary movement expected at the primary defect.</p>

- Tissue may be directly connected to the defect or nearby but not contiguous
- Usually performed when a primary straight-line closure is not possible (owing to excess tension or potential anatomic/functional distortion)
- A secondary defect is always created
- May be categorized by the following characteristics
 - Location with respect to the surgical defect (i.e., local, regional, or distant)
 - Movement (i.e., advancement, rotation) {NOTE: In reality, flaps may have more than one movement}



FIGURE 25-20 Paramedian forehead flap (supratrochlear artery). (Reproduced with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th ed. New York: McGraw-Hill; 2003.)

- Vascular supply (i.e., random pattern, axial, or microvascular)
- Stage (i.e., single or multi-stage)
- Configuration (i.e., note, rhomboid, bilobed, banner, etc.)
- Eponym (i.e., Abbé, Rieger, Mustarde, etc.)
 - No single classification accounts for every design or definition variation
 - Eponyms should generally be avoided
 - Most flaps in cutaneous surgery are local (adjacent and contiguous skin) and regional (nearby but not directly adjacent)
 - Within this context, the most useful classification scheme is based on *movement* and *vascular supply*

- Definition of terms: general
- *Tension vector*: the direction of pull or stress on a wound during its closure
- *Primary defect*: the wound that requires closure
- *Secondary defect*: the wound that results from closure of the primary defect
- *Primary movement*: the motion (advancement, rotation, or transposition) and tension vectors required for closure of the primary defect. Rotation and transposition flaps have in common a pivoting or arclike motion, whereas advancement flaps have a sliding motion in straight lines
- *Secondary movement*: the motion and tension vectors required to close the secondary defect
- *Burow's triangle (dog-ear, standing cutaneous cone)*: redundant skin that is removed as wounds are closed
- *Primary Burow's triangle*: The dog-ear directly connected to the primary defect that is removed during closure
- *Secondary Burow's triangle*: the dog-ear directly connected to the secondary defect that is removed during closure
- *Subunit*: a surface area demarcated by either natural or arbitrary lines that has unique textural, cosmetic, or functional characteristics (i.e., upper lip has four subunits: bilateral upper cutaneous lip, philtrum, and mucosal lip). In general, repairs within a subunit or incisions placed at junctions of subunits yield the best cosmetic results
- *Local flap*: adjacent and contiguous
- *Regional flap*: nearby but not directly adjacent
- *Advancement flap*: a random-pattern flap where the primary flap movement is linear and provides the least mobility among the different flap types
- *Rotation flap*: a random- or axial-pattern flap where the donor tissue pivots in a curved or arclike motion
- *Transposition flap*: a subset of either a rotation or advancement flap where the donor tissue is nearby but not directly adjacent to defect. The flap, therefore, must move across and over an intervening segment of normal skin to close the defect
- *Interpolation flap*: a subset of transposition flap that is usually indicated for larger defects and typically requires at least two separate stages of surgery (usually separated by 3 weeks between stages) (i.e., melolabial interpolation flap, paramedian forehead flap)
- *Island pedicle flap (IPF)*: a random-pattern flap where the flap is completely separated from the surrounding skin (literally an island) and subcutis except for an underlying subcutaneous pedicle. Classically, IPFs are considered advancement flaps but practically/both advancement and rotation

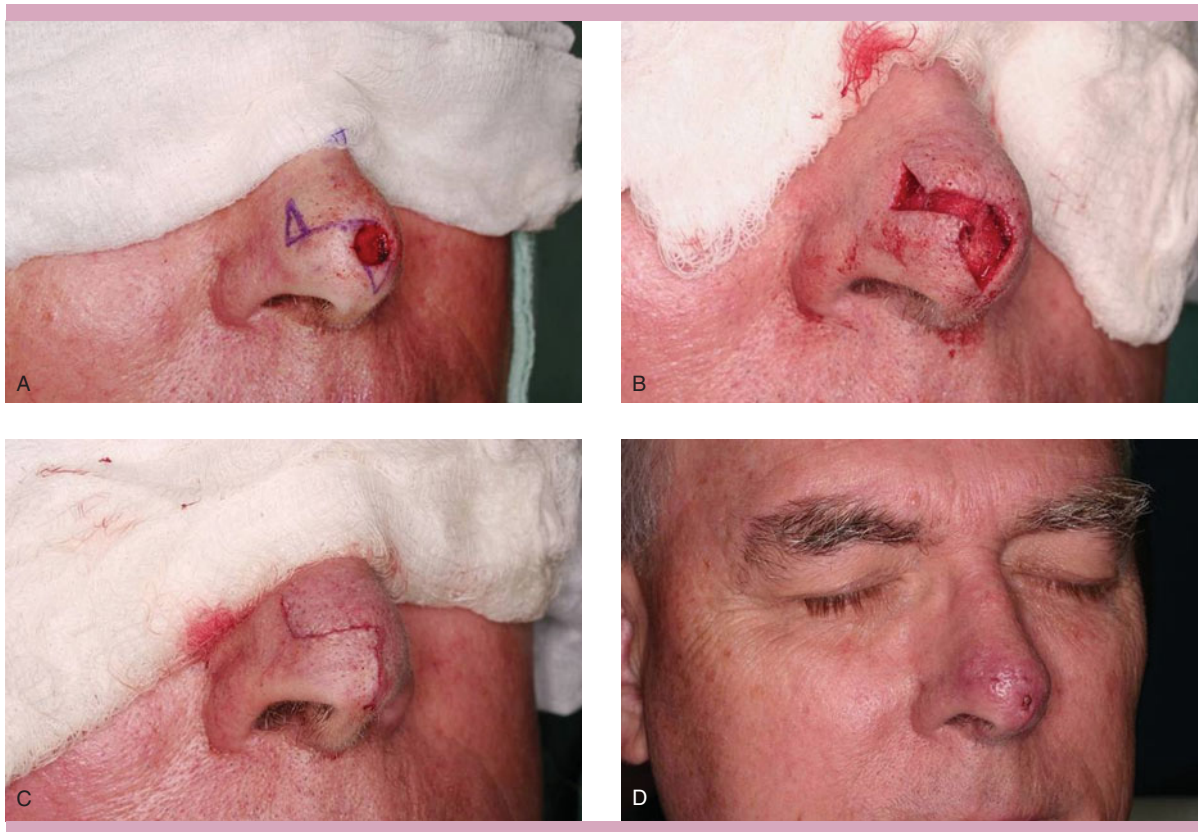


FIGURE 25-21 Burow's wedge advancement flap.



FIGURE 25-22 Crescentic advancement flap.

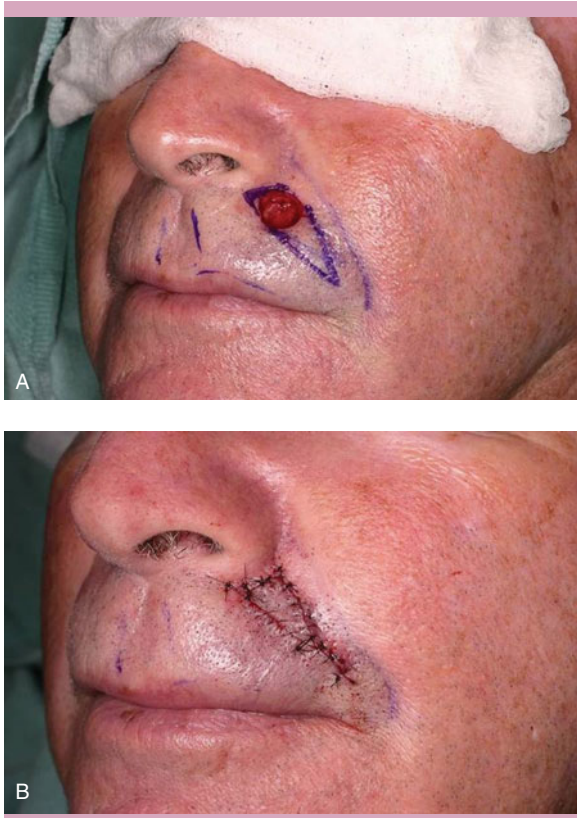


FIGURE 25-23 V to Y or island pedicle flap.

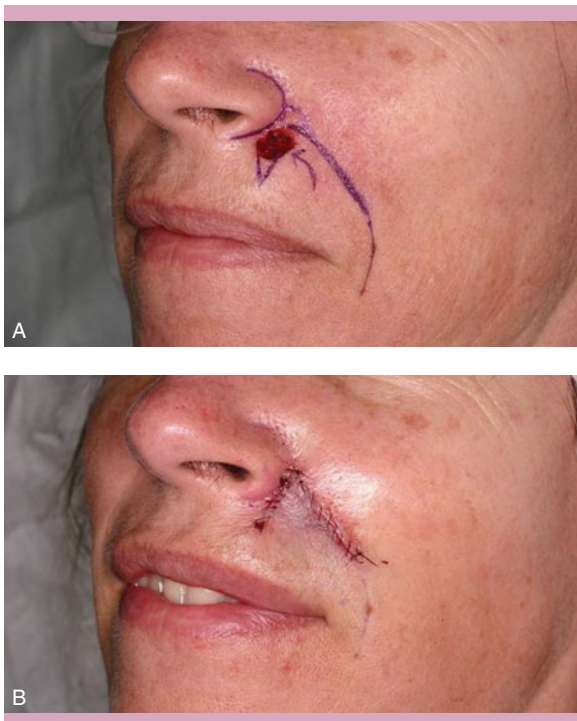


FIGURE 25-25 Rotation flap.



FIGURE 25-24 A to T bilateral advancement.
(Reproduced with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th ed. New York: McGraw-Hill; 2003.)

movements are involved, including even transposition movements. V to Y advancement is a type of IPF

- **Backcut:** a relaxing incision on the far end of a rotation curve to release lateral flap restraints and facilitate movement
- **Z-plasty:** distinct form of transposition often used for scar revision for scar length and changing scar orientation (Table 25-24)
 - Change (redirection) of tension vectors of the original wound/scar
 - Lengthening and breaking up of a scar into multiple zigzag lines. The extent of scar lengthening depends on the degree of transposition of the Z-plasty
- **Pedicle:** the vascular supply to a flap (blood vessels are contiguous with the flap)
- **Random-pattern flap:** flap that is nourished by unnamed vessels from underlying arterial perforators. Random flaps rely on a rich vascular plexus of subcutaneous tissue that directly connects with the flap
- **Axial-pattern flap:** flap that has a named vessel for its pedicle
 - Paramedian forehead flap (supratrochlear artery) (Fig. 25-20)
 - Cheek interpolation flap (angular artery)
- **Abbé (lip-switch) flap:** inferior or superior labial arteries

GRAFTS (TABLES 25-25 AND 25-26)

- Autologous skin grafts
- Skin that is detached completely from its blood

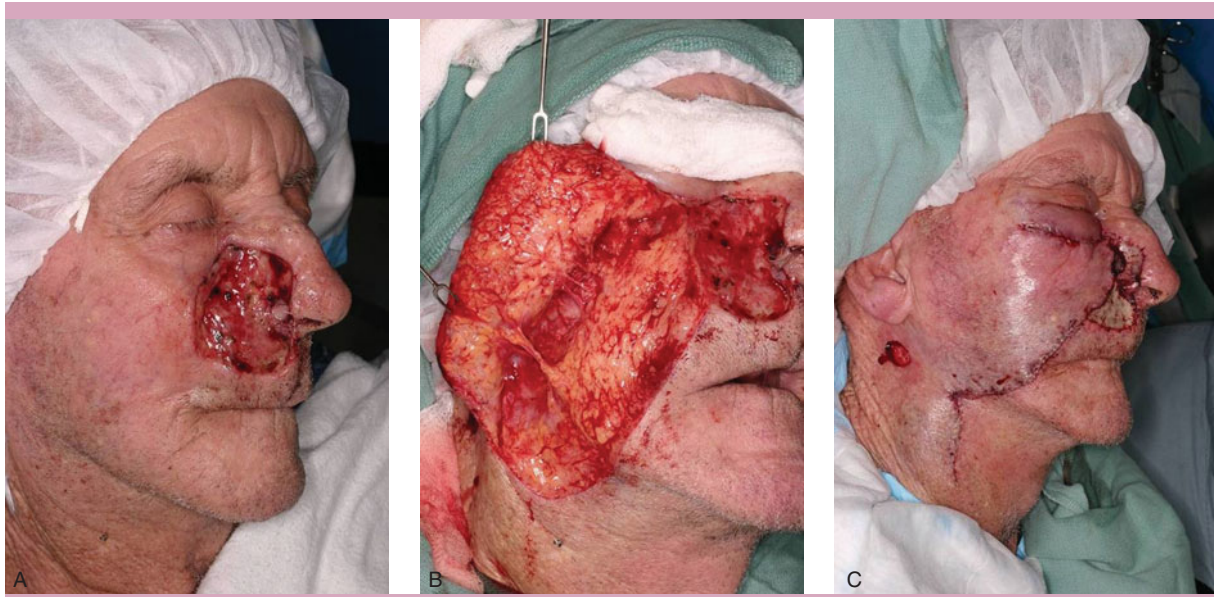


FIGURE 25-26 Cervicofacial rotation flap.

supply, removed from its donor site, and transplanted to a recipient site for wound closure in the same individual

- All grafts contract to some degree, but contraction is greatest with split-thickness skin grafts
- Graft survival depends on the establishment of new vasculature between the wound recipient site and the donor graft

LOCAL ANESTHESIA (TABLES 25-27 TO 25-29)

- Mechanism of action
 - Anesthetics block membrane Na^+/K^+ channels, thus preventing effective depolarization and nerve transmission
 - Unmyelinated C-type nerve fibers (slow conduction) conduct temperature and pain (blocked more easily)
 - Myelinated A-type fibers (fast conduction) carry pressure and motor fibers
- Side effects
 - Vasovagal reaction with hypotension and bradycardia (most frequent)
 - Place patient in Trendelenburg position to increase cerebral perfusion; supportive care; atropine for severe reactions
 - Bruising and edema, especially in periorbital area
 - Transient motor nerve paralysis
 - Prolonged paresthesia (nerve injury can occur in nerve blocks if needle traumatizes nerve)
- Allergy to anesthetic
 - True allergy is rare (more common with esters than amides)
 - Allergic reactions are usually IgE-mediated type I reactions with urticaria, angioedema, or anaphylaxis with hypotension and tachycardia
- Cocaine (ester group) is vasoconstricting; all other anesthetics are vasodilating
- Longer-lasting anesthetics (> 2 hour duration) are more protein bound (bupivacaine, etidocaine)
- Lidocaine 1% with 1:100,000 epinephrine
 - Most common local anesthetic for skin surgery
 - Very acidic (low pH)
 - Addition of NaHCO_3 to lidocaine with epinephrine neutralizes solution, reducing burning on injection and facilitating anesthetic diffusion
- Lidocaine toxicity
 - Maximum dose of lidocaine: 5 mg/kg of 1% lidocaine plain; 7 mg/kg of 1% lidocaine with 1:100,000 epinephrine
 - Systemic lidocaine toxicity: starts with circumoral numbness and tingling; can progress to seizures and cardiovascular collapse with severe overdose; toxic effects are exacerbated by acidosis and hypoxia
- Prilocaine toxicity
 - Metabolizes to ortho-toluidine, an oxidizing agent capable of converting hemoglobin to methemoglobin, potentially causing methemoglobinemia

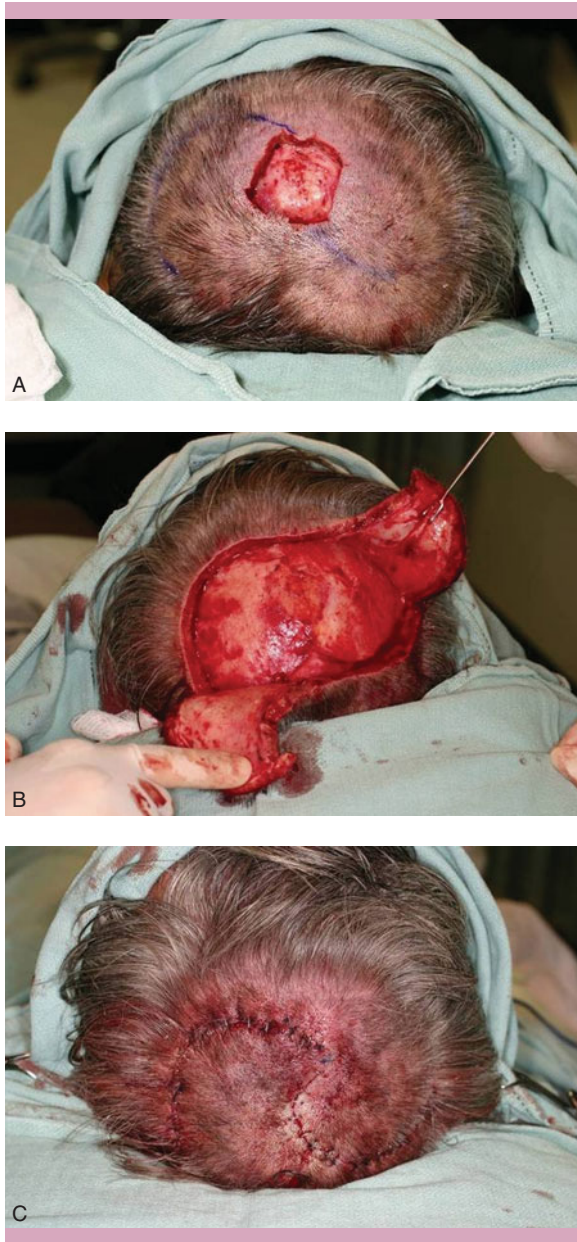


FIGURE 25-27 O to Z bilateral rotation flap.

- Patients at risk of methemoglobinemia include
 - Patients < 1 year old
 - Patients with G-6-PD deficiency
 - Methemoglobinemia-inducing agents: dapsone, nitroglycerin, nitrofurantoin, antimalarials, sulfonamides, phenobarbital, phenytoin, nitroprusside, acetaminophen
 - See EMLA below
- Bupivacaine toxicity
 - Risk of cardiac toxicity, with ventricular arrhythmias and cardiovascular collapse



FIGURE 25-28 Note or banner flap.

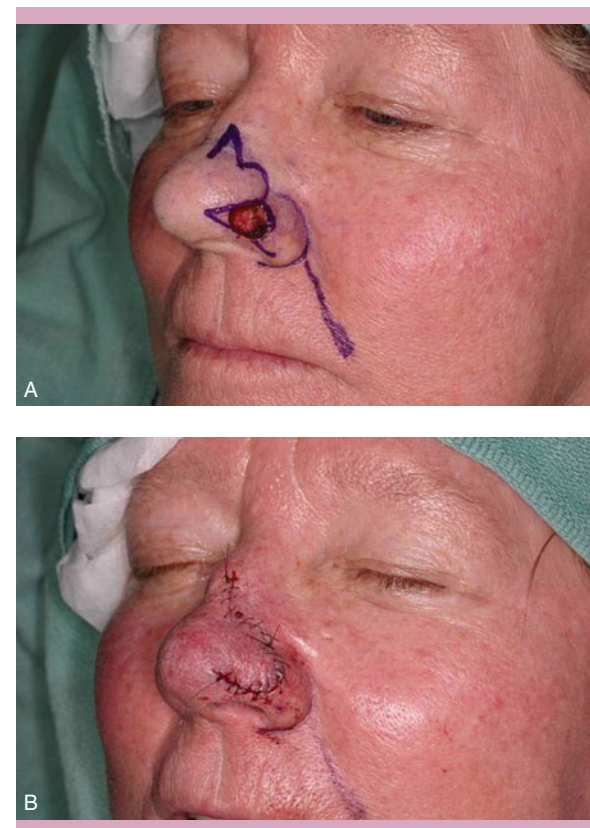


FIGURE 25-29 Bilobe flap.



FIGURE 25-30 Trilobe flap.



FIGURE 25-31 Cheek-to-nose interpolation flap.

- Epinephrine
 - Epinephrine prolongs duration of anesthesia by 100% to 150% and decreases the anesthetic's systemic toxicity by slowing absorption
 - Epinephrine is hemostatic in a dilution of up to 1:1,000,000
 - Epinephrine use in digital anesthesia (fingers/toes)
 - Safe to use in digital blocks and local anesthesia as long as these guidelines are followed
 - Epinephrine dilution of 1:200,000 or greater
 - Volumes injected are minimal (digital block should not exceed 3 mL—1.5 mL max per side)
 - Circumferential injection (ring block) is avoided
 - Patients with vascular compromise are avoided (smokers, diabetes, peripheral vascular disease, Raynaud's phenomenon)
 - Contraindications
 - Absolute: uncontrolled hyperthyroidism and pheochromocytoma
 - Relative contraindications: hypertension, blood pressure instability, severe cardiovascular disease, pregnancy, and narrow-angle glaucoma,
- beta blockers, phenothiazines, monoamine oxidase inhibitors, and tricyclic antidepressants
 - Epinephrine may be used by diluting it to 1:500,000; use sparingly
- Side effects
 - Self-limited palpitations, anxiety, fear, diaphoresis, headache, tremor, weakness, and tachycardia
 - Serious side effects: arrhythmias, ventricular tachycardia, ventricular fibrillation, cardiac arrest, and cerebral hemorrhage
- Topical anesthetics
 - Conjunctiva anesthetized with: proparacaine or tetracaine eyedrops
 - Superficial mucous membrane anesthesia: Surfacaine, Topicale, Dyclone, Anbesol, viscous lidocaine, and lidocaine jelly
 - Intranasal mucosa: 4% to 10% cocaine solution is effective, and hemostatic
 - EMLA (eutectic mixture of local anesthetics) cream contains 2.5% lidocaine and 2.5% prilocaine; applied under occlusion 1 to 2 hours preoperatively depending on location

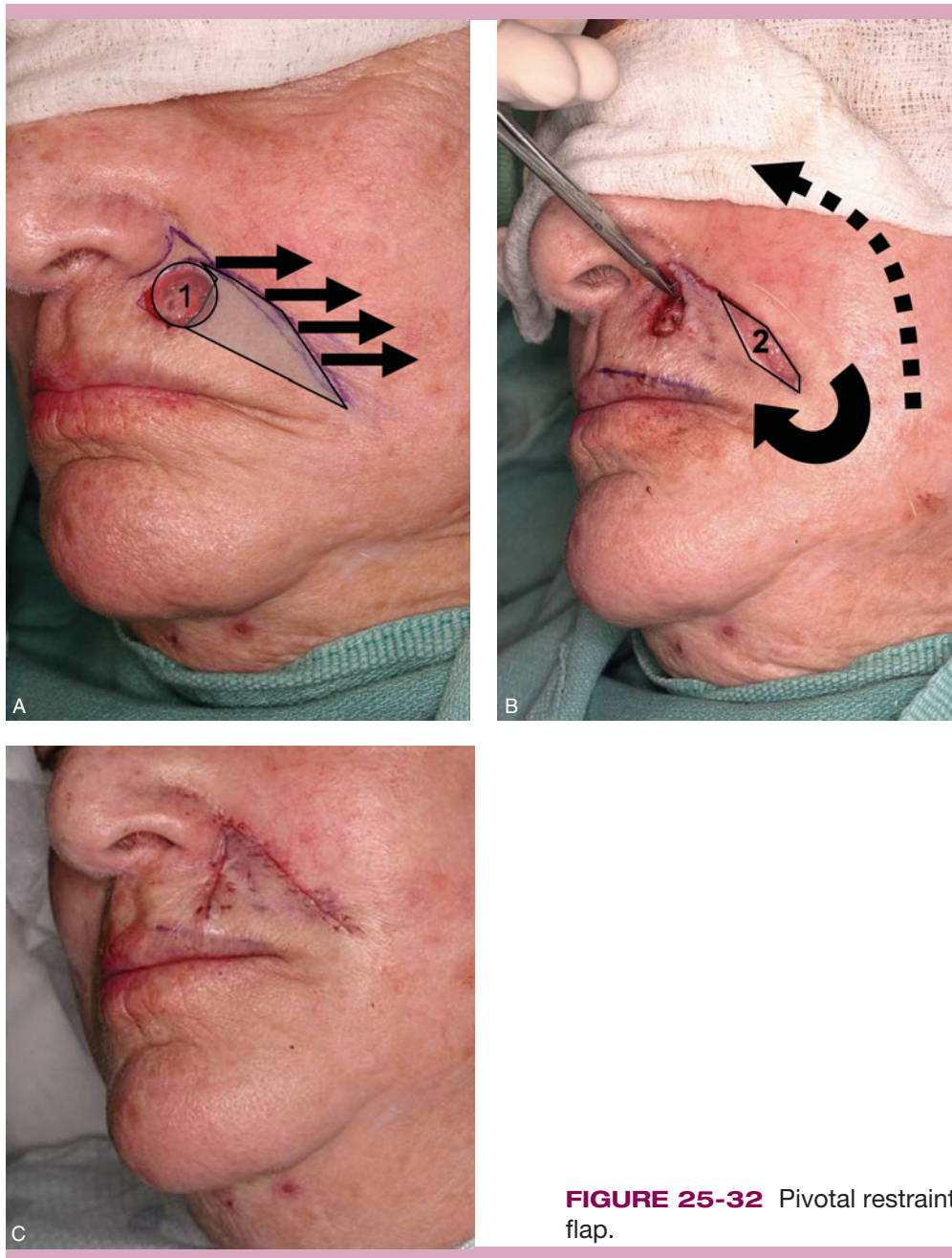


FIGURE 25-32 Pivotal restraint flap.

- Should be applied to intact skin only and in patients older than 1 year of age
- Application to denuded skin or to large surface areas may result in substantial prilocaine absorption and risk of systemic methemoglobinemia
- 30% to 40% lidocaine in acid-mantle cream may also be applied under occlusion 1 to 2 hours before a procedure
- ELA-Max (4% lidocaine) liposomal delivery; thus no occlusion necessary; no chance of methemoglobinemia as with EMLA. Available over the counter; comes in 5- and 30-g tubes
- Iontophoresis of lidocaine also can achieve superficial skin anesthesia
- Tumescent anesthesia (TA)
 - TA is the use of dilute lidocaine (i.e., 0.05% to 0.1%) and epinephrine (i.e., 1:1,000,000) for local anesthesia

- Large volumes of TA may be infiltrated subcutaneously to achieve complete anesthesia and effective hemostasis
- TA pharmacology applies only to dilute lidocaine and epinephrine; it cannot be extrapolated to other anesthetics (i.e., bupivacaine cannot be substituted for lidocaine)
- Originally developed for liposuction
- Other uses: face lift surgery, reconstruction, ambulatory phlebectomy, ablative laser resurfacing, hair transplantation, endovenous radiofrequency ablation
- Advantages of TA
 - ▲ Increases maximum safe dose of lidocaine to 55 mg/kg
 - ▲ Dilute epinephrine achieves pronounced vasoconstriction of subdermal vessels, thereby limiting systemic absorption while achieving excellent hemostasis
- Some procedures (liposuction, phlebectomy, endovenous ablation) cannot be done safely in an outpatient setting without TA
- Disadvantages of TA
 - Requires equipment and understanding of tumescent pharmacology
 - Swelling of subcutaneous space is typical but may be prolonged in the lower extremities
- Alternatives to esters and amides for local anesthesia
 - Diphenhydramine hydrochloride (Benadryl) 12.5 mg/mL
 - Normal saline injected intradermally (transient brief anesthesia)
 - Cryoanesthesia with ice or cryogen (i.e., fluoroethyl or frigiderm) for superficial procedures (i.e., dermabrasion)

SUTURE REVIEW (TABLES 25-30 AND 25-31)

- Suture characteristics (Fig. 25-33)
 - *Tensile strength*: measure of a material or tissue's ability to resist deformation and breakage
 - *Knot strength*: force required for a knot to slip
 - *Configuration*
 - Monofilament (less risk of infection)
 - Braided multifilament (easier to handle and tie)
 - *Elasticity*: degree suture stretches and returns to original length
 - *Memory or suture stiffness*: inherent capability of suture to return to or maintain its original gross shape

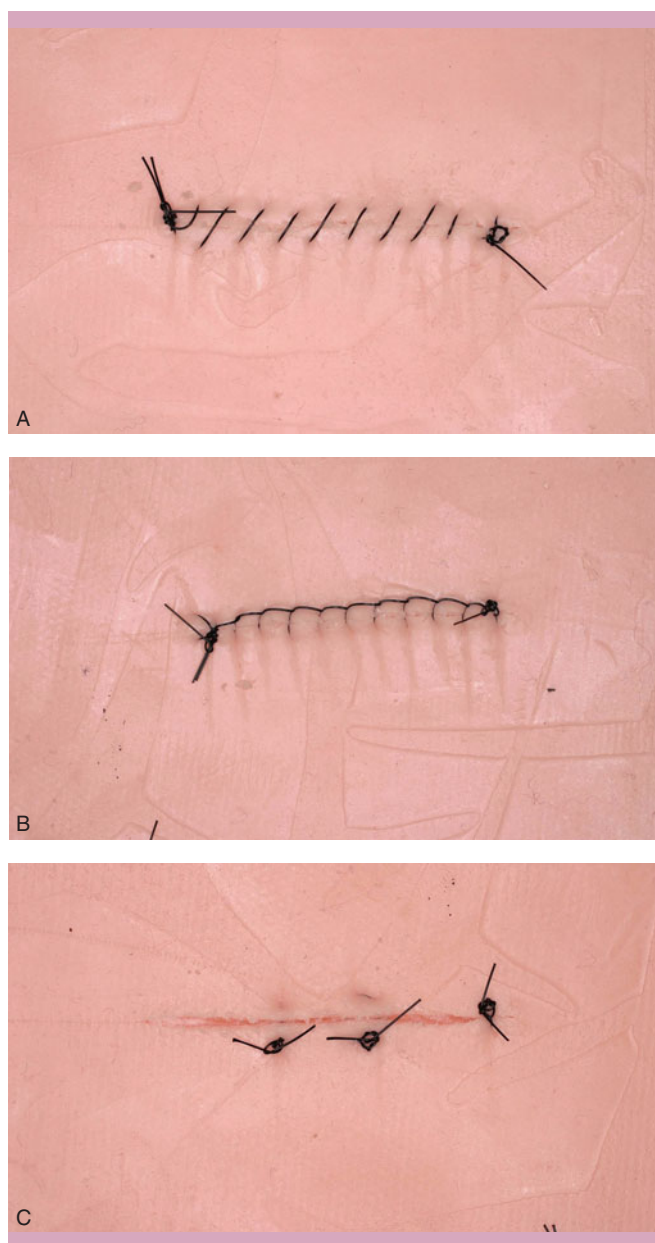


FIGURE 25-33 Suturing techniques for epidermal approximation (A) Simple running. (B) Simple running locked. (C) Vertical mattress (left), horizontal mattress (middle), and simple interrupted (right).

- *Plasticity*: measure of the ability to deform without breaking and to maintain a new form after relief of the deforming force
- *Pliability*: ease of handling of suture material; ability to adjust knot tension and to secure knots (related to suture material, filament type, and diameter)

TABLE 25-24 Z-Plasties and Scar-Lengthening Properties

Degree of Transposition	Extent of Scar Lengthening (%)
30°	25
45°	50
60°	75

TABLE 25-25 Graft Take

Phase	Timing	Comment
Plasma imbibition	First 48 hours	Imbibition means to take in or absorb fluid, causing swelling Ischemic and edematous phase of graft because no blood flow established Grafts survive the first 1 to 2 days by absorbing wound exudate and passive diffusion of nutrients. Fibin also forms between the recipient bed and graft, promoting graft adhesion and reducing infection
Inosculation	Days 2 to 3	Initial establishment of vessels between the recipient bed and graft New vessels form from the recipient bed and migrate to anastomose with vasculature from the graft Fibrin mesh established during imbibition facilitates vessel migration
Capillary ingrowth, revascularization	Days 4 to 7	Additional vascular anastomoses occur between wound base and graft Blood flow evident by days 5 to 7
Keratinocyte activation	Day 4 to week 4	Epidermal activation and proliferation, greater in split-thickness skin grafts Lymphatic flow reestablished
Sensory innervation	Begins after 2 to 3 months	Starts at edge of graft and moves centrally

TABLE 25-26 Types of Autologous Skin Grafts

	Full-Thickness Skin Graft (FTSG)	Split-Thickness Skin Graft (STSG)	Composite Grafts
Definition	Entire epidermis and a dermis harvested. Dermis may be of varying thickness depending on donor site.	Epidermis and only partial-thickness dermis Thin (0.005 to 0.012 in) Intermediate (0.012 to 0.018 in) Thick (0.018 to 0.030 in)	Contains two different tissue layers (i.e. skin and cartilage)
Advantages	Minimal contraction during healing phase. Potential for good match with recipient site if donor site properly selected. Donor site is usually sutured or closed	Much thinner, requires less metabolic support, and survives better than FTSGs. Able to cover large wounds, line cavities, resurface mucosal deficits, exposed bone, close donor sites of flaps, and resurface muscle flaps.	Provides scaffolding (cartilage) as well as soft tissue covering (skin).
Disadvantages	Donor site morbidity. FTSGs require more metabolic support (thicker) and do not survive as well as STSGs	Requires more equipment. Significant graft contraction. Cosmetically poor compared to FTSGs Discomfort and appearance of donor site (donor site heals by second intention; a rectangular discolored patch is typical postoperative appearance)	Most metabolically demanding of all graft types. Most composite grafts over 1 cm do not survive completely
Donor sites	Selected based on matching qualities for thickness, texture, pigmentation, actinic damage, and morbidity of donor harvesting (i.e., upper eyelid, nasolabial fold, pre- and postauricular regions, conchal bowl, and the supraclavicular fossa)	Harvested from any surface of the body (i.e., thigh, buttock, abdomen, scalp)	Donor site is usually crux of the helix to include skin and cartilage

TABLE 25-29 Lidocaine Toxicity

Organ System	Signs	Treatment
Central nervous system		
Early (1–5 µg/ml)	Tinnitus, circumoral pallor, metallic taste in mouth, lightheadedness, talkativeness, nausea, emesis, diplopia	Recognition, observation, hold lidocaine
Middle (8–12 µg/ml)	Nystagmus, slurred speech, hallucinations, muscle twitching, facial, hand tremors, seizures	Diazepam, airway maintenance
Late (20–25 µg/ml)	Apnea, coma	Respiratory support
Cardiovascular system	Myocardial depression, bradycardia, atrioventricular blockade, ventricular arrhythmias, vasodilation, hypotension	Oxygen, vasopressors, cardiopulmonary resuscitation
Allergy	Pruritus, urticaria, angioedema, nausea, wheezing, anaphylaxis	Antihistamines; epinephrine 0.3 ml 1:1000 SQ, oxygen, airway
Psychogenic	Pallor, diaphoresis, hyperventilation, lightheadedness, nausea, syncope	Trendelenburg position, cool compresses, observation

TABLE 25-30 Suture Materials

Material (Trade Name)	Type	Memory	Tissue Reactivity	Tensile Strength Half-Life
Nonabsorbable				
Cotton	Twisted	Low	Very high	—
Nylon (Ethilon, Demalon)	Monofilament	High	Low	—
Nylon (Nurolon, Surgilon)	Braided	Low	Low	—
Polybutester (Novafil)	Monofilament	High	Low	—
Polyester, uncoated (Mersilene)	Braided	Low	Low	—
Polyester, coated (EthiGoodd)	Braided	Very high	Very low	—
Polypropylene (Prolene, Surgilene)	Braided	Very low	High	—
Silk	Monofilament	Very high	Very low	—
Stainless steel	Braided/twisted			
	Monofilament/			
	braided/twisted			
Absorbable				
Gut, fast absorbing/mild chromic	Twisted	Very high	High	2 days
Gut	Twisted	Very high	High	4 days
Gut, chromic	Twisted	Very high	High	1 week
Polyglactin 910 (Vicryl)	Braided	Very low	Low	2 weeks
Polyglycolic acid (Dexon)	Braided	Very low	Low	2 weeks
Poliglecaprone 25 (Monocryl)	Monofilament	Low	Very low	1 week
Polyglyconate (Maxon)	Monofilament	Low	Very low	1 month
Polydioxanone (PDS)	Monofilament	High	Very low	1 month

From Weitzul S, Taylor RS: Suturing techniques and other closure materials, in Robinson JK, Hanke WC, Sengelmann RD, et al., eds., *Surgery of the Skin: Procedural Dermatology*. London: Elsevier; 2005.

TABLE 25-31 Epidermal Suture Applications

Suture Technique	Comments
Simple running	Fast epidermal closure May not approximate skin as precisely as simple interrupted May unravel if one segment is severed
Simple interrupted	Time-consuming Best for correcting minor differences in overlapping edge Most accurate for skin approximation
Vertical mattress	Suture line perpendicular to wound edge Time-consuming Best suture for additional wound edge eversion May strangulate wound edge if tied too tightly
Horizontal mattress	Suture line parallel to wound edge Time-consuming Moderate wound edge eversion Helpful in hemostasis for nonspecific wound edge oozing
Running subcuticular	Entire suture is buried in the superficial dermis except for an entry and exit point on either ends of the wound edge Time-consuming Beneficial for closure that requires epidermal support greater than 1 week; running subcuticular suture may be left in place greater than 1 week and removed later without railroad tracks on skin
Note: All epidermal sutures will leave cross-marks of railroad-track lines on skin if not removed within 1 week.	

QUIZ

Questions

1. Where do the internal carotid and external carotid arteries *not* anastamose?
- A. Perinasal
 - B. Glabella
 - C. Mentum
 - D. Periorbital

2. Put the following items in order from least to most sensitive to cryogen exposure:
- 1. Melanocytes
 - 2. Keratinocytes
 - 3. Fibroblasts
- A. 1, 2, 3
 - B. 1, 3, 2
 - C. 2, 1, 3
 - D. 2, 3, 1
 - E. 3, 2, 1
 - F. 3, 1, 2

3. Matching:

Patient	Wound Healing
1. Neutropenic	A. Not impaired
2. Lymphopenic	B. Impaired
3. Macrophage deficient	

4. Matching:

Term	Definition
1. Sterilization	A. Destruction of ALL infectious agents from an environment. This includes algae, bacteria, fungi, protozoa, viruses dormant endospores and poorly characterised agents such as viroids and the agents that are associated with spongiform encephalopathies
2. Disinfection	B. Refers to the removal of some microbes from an environment that may cause disease
3. Antisepsis	C. Less harsh in their action than are disinfectants

5. Matching:

Antibiotic prophylaxis	Indication
1. Keflex	A. Cutaneous defect
2. Amoxicillin	B. Mucosal defect
3. Clindamycin	C. Cutaneous defect, penicillin allergic
4. Azithromycin	D. Mucosal defect, penicillin allergic

6. How much will a scar lengthen with a 60-degree Z-plasty transposition?

- A. 10%
- B. 25%
- C. 50%
- D. 55%
- E. 75%

7. Which of the following is *not* a risk factor for a patient developing methemoglobinemia while using topical EMLA?

- A. Patient < 1 year old
- B. Patient with G-6-PD deficiency
- C. Patient with sickle cell anemia
- D. Patient taking dapsone
- E. Patient taking phenobarbital

8. When does inosculation occur after skin graft placement?

- A. First 48 hours
- B. Days 2 to 3
- C. Days 4 to 7
- D. Day 4 to week 4
- E. After 2 to 3 months

9. How is procaine metabolized?

- A. Pseudocholinesterase
- B. Microsomal liver enzymes
- C. Monoamine oxidase
- D. Peroxidase
- E. Glutathione s-transferase

10. Which nonabsorbable suture has more tissue reactivity?

- A. Polypropylene
- B. Silk
- C. Polyglactin 910
- D. Gut

11. Which absorbable suture has less tissue reactivity?

- A. Polypropylene
- B. Silk
- C. Polyglactin 910
- D. Gut

Answers

1. C. Mentum. Blood supply to the head and neck is via the internal carotid artery (ICA) and external carotid artery (ECA) and their branches. Intimate anastomoses between ICA and ECA occur in the region of the upper central face (nose, glabella, peri-orbital, and forehead). These connections are important clinically in that: (1) infections in this area may extend intracranially via ICA; (2) steroid injections in the periorbital skin may embolize to the retinal artery and cause blindness.
2. E. 3, 2, 1 (fibroblast, keratinocyte, melanocyte). Different cells and tissues demonstrate a range of temperature sensitivity. Melanocytes are more sensitive than keratinocytes, and with cold injury, dyspigmentation should be discussed as an adverse outcome when treating dark skinned individuals.

- Fibroblasts and other stromal structures are less sensitive to cold, which may contribute to the lack of scarring after superficial cold injury and/or cryosurgery.
3. 1, A; 2, A; 3, B. The inflammatory response is an important component after wounding of the skin. Macrophages are the most important cells for wound healing, releasing numerous growth factors and cytokines. Neutropenic or lymphopenic patients do not have impaired wound healing, whereas macrophage-deficient (quantity or function) patients heal poorly.
 4. 1, A; 2, B; 3, C. Infection control is extremely important to prevent infection. Techniques used to destroy all infectious agents from an environment is called sterilization. In contrast, disinfection and antisepsis are terms that should be used to reduce microbe burden, with disinfection utilizing harsher agents that, in general, would not be used on human tissue (i.e., undiluted bleach).
 5. 1, A; 2, B; 3, C,D; 4, C,D. Although the risk of wound infection after skin surgery is small (1–2%), routine prophylactic antibiotics are usually indicated for: 1) certain patient populations: immunosuppressed, debilitated patients, and those with reduced blood flow to the surgical site (i.e., peripheral vascular disease, diabetes mellitus); 2) anatomic sites at greater risk for infection: ears, perineum, legs, and feet. Prophylactic antibiotic regimen depends on the endogenous flora of the operative site, as well as, patient specific issues (i.e., penicillin allergic).
 6. E. 75%. The Z-plasty is a form of transposition flap that is often used for scar revision for scar length and changing scar orientation. It alters the change (redirection) of tension vectors of the original wound/scar, in addition to lengthening and breaking up of a scar into multiple zigzag lines. The extent of scar lengthening depends on the degree of transposition of the Z-plasty.
 7. C. Sick cell anemia. EMLA (eutectic mixture of local anesthetics) cream contains 2.5% lidocaine and 2.5% prilocaine. Prilocaine is metabolized to ortho-toluidine, an oxidizing agent capable of converting hemoglobin to methemoglobin, potentially causing methemoglobinemia. Patients at risk of methemoglobinemia include: patients < 1 year old, patients with G-6-PD deficiency, and patients taking methemoglobinemia-inducing agents (dapsone, nitroglycerin, nitrofurantoin, antimalarials, sulfonamides, phenobarbital, phenytoin, nitroprusside, acetaminophen).
 8. B. Day 2 to 3. A skin graft is any skin that is detached completely from its blood supply, removed from its donor site, and transplanted to a recipient site for wound closure in the same individual. Graft survival depends on the establishment of new vasculature between the wound recipient site and the donor graft through the following phases: imbibition, inosculation, capillary ingrowth and neovascularization, keratinocyte activation, and finally, sensory innervation.
 9. A. Pseudocholinesterase. Several major enzymes and pathways are involved in drug metabolism. Amide anesthetics are N-dealkylated and hydrolyzed by microsomal liver enzymes cytochrome P450 3A4. Ester anesthetics are hydrolyzed by tissue pseudocholinesterases and excreted by kidney. Procaine is an ester anesthetic.
 10. B. Silk. Suture characteristics include: tensile strength, knot strength, configuration, elasticity, memory or suture stiffness, plasticity, and pliability. Suture reactivity is another characteristic defined as the amount of inflammatory response that is elicited, which is dependent on the material from which it is made. Synthetic sutures are made from synthetic collagen derived from polymers and are broken down by hydrolysis as opposed to enzymatic degradation in natural sutures, causing less tissue reaction. In contrast, natural sutures are made from natural materials such as collagen derived from the gastrointestinal track of animals, woven cotton, raw silk, linen, or steel. Of the answer choices listed, polypropylene and silk are non-absorbable suture made from synthetic and natural materials, respectively.
 11. C. Polyglactin. Suture characteristics include: tensile strength, knot strength, configuration, elasticity, memory or suture stiffness, plasticity, and pliability. Suture reactivity is another characteristic defined as the amount of inflammatory response that is elicited, which is dependent on the material from which it is made. Synthetic sutures are made from synthetic collagen derived from polymers and are broken down by hydrolysis as opposed to enzymatic degradation in natural sutures, causing less tissue reaction. In contrast, natural sutures are made from natural materials such as collagen derived from the gastrointestinal track of animals, woven cotton, raw silk, linen, or steel. Of the answer choices listed, polyglactin 910 and gut suture are absorbable suture made from synthetic and natural materials, respectively.

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COSMETIC DERMATOLOGY

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SKIN AGING

- Intrinsic: natural aging, genetic process
- Extrinsic: exogenous causes; ultraviolet radiation, smoking
- Photoaging: skin is changed or damaged as a result of exposure to ultraviolet radiation in sunlight and other sources
 - Long-term effects include
 - Wrinkles
 - Discoloration
 - Telangiectasia
 - Susceptibility to cancer
 - Solar elastosis (heliosis): term applied to the chronic inflammatory changes and degradation of elastin and collagen

PHOTOAGING

- Glogau photoaging classification
 - Qualitative visual grading system (Table 26-1)
- Fitzpatrick skin types: classification of a patient's cutaneous reaction to ultraviolet skin exposure. The lower the skin type number, the greater the susceptibility to photoaging. (Table 26-2)
- Molecular mechanism of photoaging
 - UV light activates activator protein 1 (AP-1)
 - AP-1 upregulates extracellular matrix (ECM)-degrading metalloproteinases (MP)
- Molecules related to aging
 - Extracellular signal-regulated kinase (ERK): photoaging
 - c-Jun NH₂-terminal kinase (JNK): natural aging
 - UV light: generates hydroxyl radicals, damages DNA

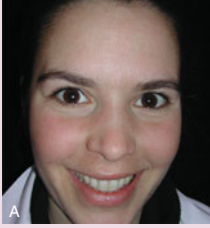

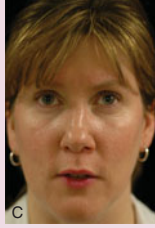

- Blocks transforming growth factor β (TGF- β) receptor II gene; prevents procollagen promoter with a reduction of collagen formation
- Telomeres and aging skin
 - *Telomeres*: tandem repeats of the DNA base sequence (TTAGGG) (T-thymine, G = guanine, A = adenosine), at the end of mammalian chromosomes, telomere extension occurs by the action of telomerase (Fig. 26-1)
 - DNA polymerase does not copy the final bases on each chromosome, resulting in telomere shortening after each round of cell division
 - When the telomeres become too short, the cell will no longer divide
 - 3' telomeric overhang (T-oligos): 3'-guanine-rich single-stranded overhang that is concealed in a protective loop
 - Most important: telomeric repeat binding factor 2 (TRF2)
 - Exposed during DNA damage or progressive telomere shortening
 - T-oligos: taken up into the nucleus and recognized by a sensor; initiates DNA damage signaling

ELECTROMAGNETIC RADIATION

Light Properties

- A quanta of light energy is a photon
- Photons display duality: both particle-like and wave-like behavior
- Electromagnetic radiation (EMR): form of energy, moves through space as a wave and comprised of photons, organized along an electromagnetic spectrum (Table 26-3 and Fig. 26-2)

TABLE 26-1 Glogau Photoaging Classification

Glogau Photoaging Scale	I (Mild)	II (Moderate)	III (Advanced)	IV (Severe)
				
Type of photoaging	Early photoaging	Early to moderate	Advanced	Severe
Age (years)	20s-30s	Late 30s-40s	50s or greater	60s or greater
Rhytids	None	Dynamic (present in motion) Slight lines near the eyes and mouth	Static (present at rest) Visible wrinkles all the time	Numerous rhytids
Cutaneous appearance and lesions	Minimal to no discoloration No keratoses (skin overgrowths)	No visible keratoses	Noticeable discolorations Visible keratoses	Yellow or gray color to skin Prior skin cancer

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TABLE 26-2 Fitzpatrick Skin Types

Skin Type	I	II	III	IV	V	VI
Clinical appearance	Very white or freckled	White	White to olive	Brown	Dark brown	Black
Burns?	Always burns	Usually burns	Sometimes burns	Rarely burns	Very rarely	Never burns
Tans?	Never tans	Some ability to tan	Easily tans	Always tans	Always tans	Always tans

- Photon energy is proportional to wave frequency and inversely related to wavelength
- Ultraviolet (UV) light is part of the electromagnetic spectrum. UVA and UVB light has physiologic effects on the skin; UVC is filtered by the ozone layer (Table 26-4)

LASER Properties

- LASER (Light amplified by stimulated emission of radiation)
- LASER is a form of electromagnetic radiation
 - Characteristics of lasers (Table 26-5)
 - *Monochromaticity*: single, discrete wavelength. Active medium determines the emission

wavelength, which is restricted to a very narrow band

- *Coherency*: monochromatic light in phase. Highly directional
- *Collimation*: light in parallel fashion to achieve its propagation across long distances without light divergence (constant diameter beam)
- *Intensity*: amplification process allows the emission of high-energy level laser

Chromophores

- Skin components that absorb the laser light
 - *Endogenous*: water, melanin, protein, and hemoglobin

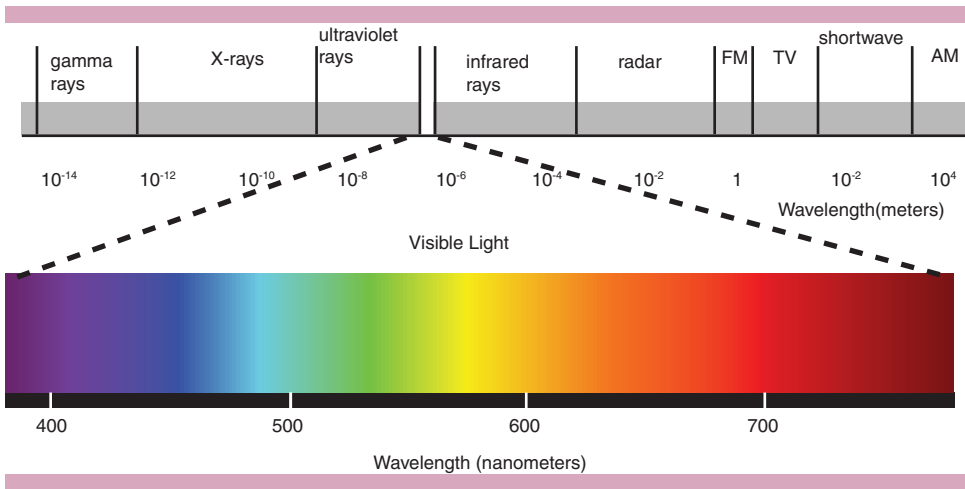


FIGURE 26-2 Electro-magnetic spectrum.

TABLE 26-4 Ultraviolet Light Characteristics

	Ultraviolet C Light (UV-C)	Ultraviolet B Light (UV-B)	Ultraviolet A Light (UV-A)
Wavelengths	<ul style="list-style-type: none">• 100 to 290 nm	<ul style="list-style-type: none">• 290 to 320 nm	<ul style="list-style-type: none">• UV-A I: 340 to 400 nm• UV-A II: 320 to 340 nm
Characteristics	<ul style="list-style-type: none">• Most dangerous type of UV light• Cannot penetrate Earth's ozone layer	<ul style="list-style-type: none">• Photons 1000 times more energetic than UV-A• Absorbed by the epidermis, approximately 10% penetrating to deeper layers of the skin• Causes acute sunburn, skin cancer	<ul style="list-style-type: none">• 10-fold greater abundance in terrestrial sunlight compared to UV-B• Approximately 50% of UV-A radiation penetrates the epidermis and reaches the papillary dermis• Causes delayed tanning

TABLE 26-5 LASER Characteristics

LASER Characteristic	Symbol	Unit of Measurement
Wavelength	λ	Nanometer (nm)
Spot size	d (diameter) s (square)	Centimeter (cm)
Pulse duration	T (exposure time)	Seconds (sec)
Power output	P (power) Energy delivery per unit time	Watts (W) = Joules/sec (J/sec)
Fluence	Φ Energy delivery per unit area	Joules/cm ² (J/cm ²)
Irradiance (not to be confused with intensity)	Power delivered per unit area	W/cm ²

- *Exogenous*: tattoo ink
- Lasers effects on tissue components (chromophores) depend on absorption spectra (Fig. 26-3)

Skin Optics

- *Reflection*: waves encounter a surface or other boundary that does not absorb the energy of the radiation and bounces the waves away from the surface
- *Absorption*: energy is deposited in a chromophore
- *Scattering*: energy is redirected elsewhere in the skin, dermal light scattering varies inversely with wavelength
- *Tyndell effect*: short (blue) wavelengths are scattered more than long (red) wavelengths
- *Transmission*: direction of photon path is unchanged

Depth of Penetration

- Depends on absorption and scattering
- Depth of penetration increases with wavelength
 - Amount of scattering of laser energy is inversely proportional to the wavelength of incident light

Laser-Tissue Interactions

- *Photothermal reaction*: various effects on the skin occur directly from heat (Table 26-6)
- *Photochemical reaction*: reaction of an endogenous or exogenous photosensitizer with UV or visible light
- *Photomechanical reaction*: rapid absorption of a laser pulse resulting in a rapid temperature change along with sudden tissue vaporization, shock wave, or pressure wave formation
- Selective photothermolysis
 - Controlled destruction of a targeted lesion without significant thermal damage to surrounding normal tissue

- Thermal damage can be induced in tissue targets that absorb photons well at the emitted wavelength
- Pulse duration or exposure time should be shorter than the cooling time or thermal relaxation time (defined as the time required for the targeted site to cool to one-half its peak temperature immediately after laser irradiation) of the target

Laser Media (Fig. 26-4)

- Laser beam wavelength is determined by the lasing medium (Tables 26-7 and 26-8)
 - *Solid-state lasers*
 - Lasing material distributed in a solid matrix
 - Ruby or neodymium:yttrium-aluminum garnet (Nd:Yag) lasers
 - *Gas lasers*
 - Primary output of visible red light
 - Helium and helium-neon (HeNe)
 - *Excimer lasers*
 - Name is derived from the terms excited and dimers
 - Use reactive gases, chlorine and fluorine, mixed with inert gases such as argon, krypton, or xenon
 - When electrically stimulated, a pseudo-molecule (dimer) is produced
 - When lased, the dimer produces light in the ultraviolet range
 - *Dye lasers*: use complex organic dyes
 - *Semiconductor lasers* (diode lasers)
- Laser treatment for tattoo, pigment, and vascular lesions are describe in Tables 26-9–26-11
- The differences between ablative, nonablative, and fractional skin resurfacing are described in Tables 26-12 and 26-13

Non-Laser Light Sources

- Intense pulsed light (IPL)
 - Noncoherent light within 500 to 1200 nm

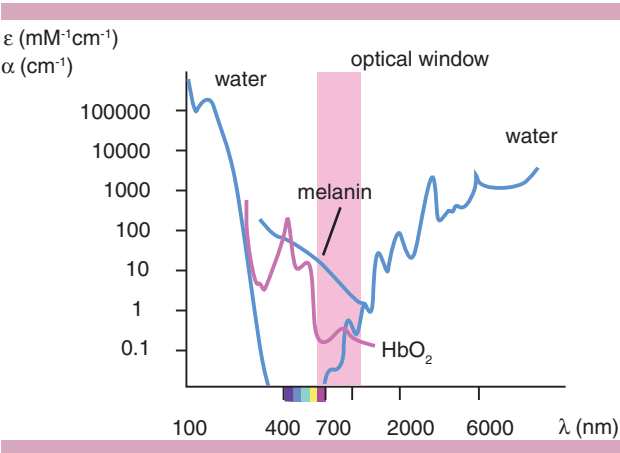
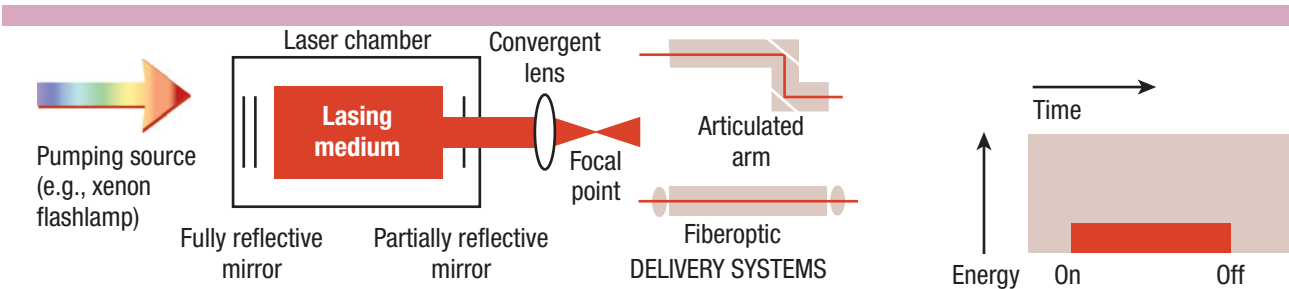


FIGURE 26-3 Absorption spectra of cutaneous chromophores.

TABLE 26-6 Thermal Effects on Skin Cells

Temperature	Thermal Effect
Increase of 5 to 10°C	Cell injury and inflammation
Above 60°C	Denaturation of protein
Above 70°C	Denaturation of DNA
Over 100°C	Vaporization of water (Boiling point of water = 100°C)

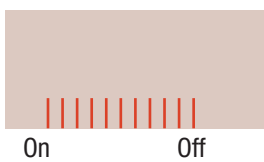


A. Schematic of a typical laser light source. Electrical, chemical, or optical energy input is provided by the pumping source. Note that the initial wavelength of the emitted laser beam is determined by the lasing medium, although this can be altered. Laser energy is delivered to the target via an articulated arm or fiberoptic cable.

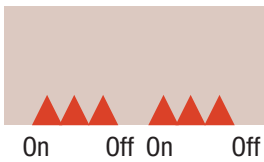
B. Continuous wave (CW) mode profile, (e.g., CO₂, argon lasers)



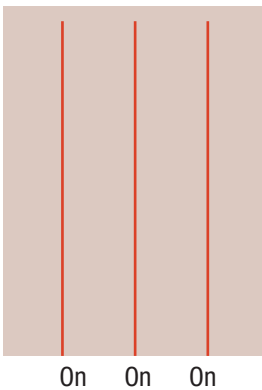
C. Pulsed mode profile (e.g., pulsed dye laser, diode, ruby, alexandrite)



D. Quasi-continuous wave (QCW) mode profile (e.g., KTP, copper vapor)



E. "Stuttered" pulse mode profile, as seen in long-pulsed dye lasers and IPLs.



F. Q-switched (QS) mode profile (e.g., QS ruby, Nd: YAG, alexandrite)

FIGURE 26-4 Laser beam types. (Reprinted with permission from Wolff, K et al: *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

TABLE 26-7 Laser Beam Types

	Continuous-Wave (CW) Lasers	Quasi-Continuous-Mode (QSW)	Pulsed Lasers
Mechanism of action	Continuous beam of light	Continuous-wavelength lasers that are mechanically shuttered to deliver pulses of light as short as 20 ms	Select pulse duration based on target size. Long pulse (millisecond): 0.5 to 400 ms allows for targeting of most hair and blood vessels(i.e., visible to near infrared lasers)

(Continued)

TABLE 26-7 (Continued)

	Continuous-Wave (CW) Lasers	Quasi-Continuous-Mode (QSW)	Pulsed Lasers
Characteristic	Little or no variation in power output over time (stable average beam power) Long exposure times with low peak power	Produce individual pulses of light Energy within the pulse is not constant but rather builds, peaks, and tapers off within a very short time Peak power outputs of pulsed lasers are often up to 100 times the maximum output of CW lasers	<i>Short pulse (microsecond)</i> : modified to produce very short pulses with high peak power in a repetitive fashion; developed to reduce the amount of thermal damage that occurs adjacent to a vaporized area or a laser incision; when applied to CO ₂ laser, allows for much safer skin resurfacing (i.e., CO ₂) <i>Q-switched (QS) (nanosecond)</i> : allows buildup of extremely high energy in the laser cavity before discharge in very short single pulses. (Q stands for the quality factor of the laser cavity and represents the rate of discharge of energy of quality-switched lasers.) (i.e., alexandrite, ruby, QS-Nd:YAG)
Complications	Can result in non-selective tissue injury (scar) as heat spreads from chromophore	Lower the risk of thermal injury to surrounding non-targeted structures	
Examples	CO ₂ Argon	Argon-pumped tunable dye Potassium-titanyl-phosphate (KTP) Copper vapor Krypton	

TABLE 26-8 Types of Lasers and Light Sources

Laser	Wavelength (nm)	Color	Chromophore	Output
Excimer	308	Ultraviolet	Protein	QCW
Narrow-band blue light	407–420	Violet/blue	Endogenous porphyrins	CW
Argon	488/514	Blue	Vascular and pigmented lesions	CW
Pulsed dye (PDL)	510	Yellow	Pigmented lesions, vascular lesions	Pulsed
Copper vapor	511/578	Yellow/green	Pigmented lesions, vascular lesions	CW
Krypton	530/568	Yellow/green	Pigmented lesions, vascular lesions	CW
Potassium-titanyl-phosphate (KTP), Nd:YAG, frequency-doubled	532	Green	Pigmented lesions, red tattoos	QS
Argon-pumped tunable dye	577/585	Yellow	Vascular lesions	CW
Pulsed dye laser (PDL)	585–595	Yellow	Vascular lesions, hypertrophic/keloid scars, striae, verrucae, nonablative dermal remodeling	Pulsed

(Continued)

TABLE 26-8 (Continued)

Laser	Wavelength (nm)	Color	Chromophore	Output
Ruby, normal mode	694	Red	Hair removal	Pulsed
QS ruby	694	Red	Pigmented lesions, blue/black/green/tattoos	QS
Alexandrite, normal mode	755	Red	Hair removal, leg veins	Pulsed
QS alexandrite	755	Red	Pigmented lesions, blue/black/green tattoos	QS
Diode	800–810	Red	Hair removal, leg veins	Pulsed
Qs Nd:YAG	1064	Infrared	Pigmented lesions, blue/black tattoos	QS
Normal mode	1064	Infrared	Hair removal, leg veins, nonablative dermal remodeling	Pulsed
Nd:YAG	1320	Infrared	Water: nonablative dermal remodeling	Pulsed
Diode	1450	Infrared	Water: nonablative dermal remodeling	Pulsed
Erbium	2940	Infrared	Water	CW
CO ₂	10,600	Infrared	Water (vaporization and coagulation): actinic cheilitis, verrucae, rhinophyma Ablative skin resurfacing, epidermal/dermal lesions	CW Pulsed

Note: CW, continuous-wave; Nd, neodymium; QCW, Quasi continuous wave; QS, quality-switched; YAG, yttrium-aluminum-garnet.

Table 26-9 Laser Treatment of Tattoo Pigment (Chromophore Is Tattoo Ink)

Laser Type	Wavelength	Tattoo Pigment Color
Pigmented PDL	510 nm	Orange, yellow, purple
QS Nd:YAG, frequency-doubled	532 nm	Red, orange, yellow
QS ruby	694 nm	Blue, blue-black Occasionally green and brown
QS alexandrite	755 nm	Blue, black, and green
QS Nd:YAG	1064 nm	Blue-black

Table 26-10 Lasers Used for Vascular Lesions (Chromophore Is Hemoglobin)

Indication	Laser
Port-wine stain	PDL IPL
Hemangiomas	PDL
Telangiectasias	Green-light lasers (532 nm) PDL Diode laser Long-pulsed Nd:YAG (1064 nm)
Pyogenic granuloma	PDL Carbon dioxide laser, combined continuous-wave/pulsed
Angiofibromas	PDL CO ₂

TABLE 26-11 Laser Treatment of Pigmented Lesions (Chromophore Is Melanin)

Indication	Laser
Lentigines	QS ruby QS alexandrite QS Nd:YAG (532 nm) IPL
Nevus of Ota	QS ruby QS alexandrite QS Nd:YAG (1064 nm)
Congenital melanocytic nevi	Normal ruby QS ruby QS Nd:YAG (532 nm)
Café-au-lait macules	QS ruby QS Nd:YAG (532 nm) Copper vapor
Nevus spilus	Normal ruby Normal alexandrite QS ruby QS Nd:YAG (532 nm)

TABLE 26-12 Laser and Other Devices for Nonablative Remodeling

Indication	Laser	Comment
Wrinkles or acne scars	Pulsed-dye laser Nd:YAG (1064, 1320 nm) Diode (1450 nm)	Chromophore is hemoglobin Chromophore is water Chromophore is water
Nonsurgical lift	Radiofrequency	Heat from electrical resistance

TABLE 26-13 Comparative Summary of Ablative and Nonablative Skin Resurfacing and Fractional Photothermolysis

	Ablative Skin Resurfacing	Nonablative Skin Resurfacing	Fractional Photothermolysis
Chromophore	Water	Hemoglobin, melanin	Water
Mode of application	Stamping approach; bulk heating	Stamping approach: bulk heating	Uniform beam; fractional heating; tissue sparing
Mode of thermal damage	Epidermal vaporization and coagulation of underlying dermis	Thermal damage, mainly dermal	Columns of thermal damage in epidermis and dermis
Laser and light sources	CO ₂ laser (10,600 nm) Erbium: YAG laser (2,940 nm)	PDL (585–595 nm) IPL (515–1,200 nm) Q-switched Nd:YAG laser (1,064 nm) Long-pulsed Nd:YAG laser (1,320 nm) Diode laser (1,450 nm) Erbium: Glass laser (1,540 nm) Radiofrequency device	Erbium-doped fiber laser (1,550 nm) CO ₂ laser (10,600 nm) Erbium laser (2,940 nm) Nd: YAG Laser (1,440 nm)
Recovery time	Up to 6 months	Up to 1 month	1–2 weeks
Efficacy (%)	60–90%	10–80%	70–80%

(Continued)

TABLE 26-13 (Continued)

	Ablative Skin Resurfacing	Nonablative Skin Resurfacing	Fractional Photothermolysis
Adverse effects	Hyperpigmentation Hypopigmentation Erythema Pruritus Dryness Acne Milia Scarring Infection	Hyperpigmentation Hypopigmentation Erythema Scarring	Erythema Pruritus Dryness Acne

- Filtered xenon flashlamps are used to eliminate shorter wavelengths
- Single-, double-, or triple-pulse sequences; pulse durations of 2 to 25 ms and delays between pulses ranging from 10 to 500 ms
- Light-emitting diodes (LEDs)
 - Narrow-band light source (i.e., not a single wavelength)
 - Emit noncoherent light; restricted range of ± 20 nm; pulse signal to stimulate mitochondria in fibroblasts

Laser Safety

- Fire prevention with CO₂ lasers
 - Saline-soaked drapes or cloths should be used intraoperatively
 - Exposed hair-bearing areas should be kept moist; alcohol-based skin preparations should be strictly avoided
- Eye protection: permanent visual loss can result
- Aerosolized particles: smoke evacuator with clean filters and tubing

Topical Anesthetic Compounds

- Can be applied under occlusion for 30 to 90 minutes before laser treatment
- *EMLA cream* 5%: lidocaine 2.5% and prilocaine 2.5%
- *LMX*: 4% or 5% lidocaine
- *S-caine peel*: lidocaine and tetracaine
 - Applied to the skin as a cream 30 minutes before treatment
 - Dries to a thin, flexible film that can be peeled away easily
- For ablative laser skin resurfacing procedures: consider combination anesthesia (i.e., topical, tumescent, nerve blocks, sedation)

Possible Laser Side Effects

- General: dyspigmentation (most common), erythema, pain, scar, incomplete removal of target

- Laser tattoo or pigmented lesion removal: purpura, eschar
- Laser treatment of vessels: purpura, vesiculation
- Laser hair removal: perifollicular edema, vesiculation
- Ablative laser skin resurfacing
 - Short term: edema, exudation, infection (*Herpes simplex virus*, *Candida*, or bacterial)
 - Medium term: acne/milia, pruritus, hyperpigmentation, dermatitis
 - Permanent: hypopigmentation, scar, ectropion
- Nonablative resurfacing: vesiculation

Skin Cooling

- Decreases risk of vesiculation and pigmentary changes (most common) by protecting epidermis
- Methods of cooling
 - *Inert*: ice, cold gel, water-cooled glass or sapphire treatment tips
 - *Active*: forced air cooling, cryogen spray

SKIN RESURFACING CHEMICAL PEELS

- Depth of peels and peeling agents are listed in Tables 26-14 and 26-15

TABLE 26-14 Depth of Peel

Depth of Peel	Wound Characteristics
Superficial	Necrosis of all or part of the epidermis
Medium	Necrosis extends to part or all of the papillary dermis
Deep	Wounding extends into the mid-reticular dermis

TABLE 26-15 Peeling Agents

Chemical Agent	Characteristics
Alpha-hydroxy acid (AHA)	Glycolic, lactic, citric, and malic acids Dependent on the contact time with the skin Carboxylic acids normally found in many foods Thins the stratum corneum, although the epidermis thickens May increase photosensitivity
– Glycolic acid	Derived from sugar cane Concentrations range from 20% to 70% Decreases corneocyte cohesion by promoting exfoliation of the outer layers of the stratum corneum Neutralize with sodium bicarbonate Dispersal of melanin pigmentation and a return to a more normal rete pattern
– Lactic acid (LA)	Derived from sour milk Acts as a humectant (causes the skin to hold onto water), keratolytic
Beta-hydroxy acid (BHA) –Salicylic acid	Derived from willow bark, wintergreen leaves, or sweet birch Concentrations of 20% or 30% (OTC preparations contain only 2%) Exhibits anti-inflammatory capabilities, producing less irritation Lipophilic Penetrates the follicular sebaceous material (anticomedogenic effect) Does not need to be neutralized, and the frost is visible No need to time the peel: after 2 minutes, there is very little absorption of the active agent Contraindicated in pregnancy, breast-feeding, and aspirin allergies Adverse effect: salicylism (nausea, disorientation, and tinnitus)
Jessner's solution	14% salicylic acid, 14% lactic acid, 14% resorcinol in alcohol Keratolytic effects
Carbon dioxide (CO ₂)	Boiling point: 78°C Physical peeling method Solid block of CO ₂ ice dipped in an acetone-alcohol mixture Applied to the skin for 5 to 15 seconds
Resorcinol	1,3-Dihydroxybenzene Concentrations of 20% to 50%
Trichloroacetic acid	Can be used for superficial, medium, and less often deep peels No need to neutralize No systemic toxicity Causes coagulation of proteins in the skin (results in frost)
Baker Gordon phenol	Phenol 88%, 2 mL distilled water, 8 drops Septisol, and 3 drops croton oil Septisol (triclosan) causes deeper penetration of phenol and a deeper peel Croton oil (especially the toxic fraction solubilized in phenol) causes a deeper peel Exfoliation to middle reticular dermis New zone of collagen forms Occluded method uses zinc oxide tape or other artificial barrier product to prevent evaporation of the phenol from the skin, thus enabling the solution to penetrate deeper <i>Litton's formula:</i> replaces Septisol (triclosan) with glycerin <i>Beeson McCollough formula:</i> uses aggressive defatting and heavier application of Baker Gordon solution

- Indications
 - Actinic keratoses
 - Superficial scarring
 - Hyperpigmentation and melasma
 - Mild wrinkles
 - Acne
- Chemical peel strengths
 - Depend on the amount of free acid present
 - Free acid availability (pKa)
 - $pK_a = pH$ at which half is in acid form
 - Lower pKa = more free acid available
 - Affected by
 - Percentage of acid
 - Type of vehicle used
 - Buffering
 - pKa of acid preparation
 - Contact time
- Defatting
 - Acetone, rubbing alcohol, or Septisol (triclosan)
 - Essential for penetration as most agents are not lipid soluble
- Frost
 - Whitish tint of skin due to keratin agglutination
 - Dependent on pre-existing degree of photo damage, choice of applicator, adequacy of defatting
 - Level of peel can be correlated with the intensity of the frost (Table 26-16)
- Complications of chemical peels
 - Arrhythmias (need electrocardiogram and pulse oximeter monitoring with phenol peels)
 - Pigmentary change
 - Scarring
 - Infection
 - Prolonged erythema
 - Acne
 - Milia

MICRODERMABRASION AND DERMABRASION

- The differences between microdermabrasion and dermabrasion are listed in Table 26-17

BOTULINUM TOXIN (BTX)

- Mechanism of action
 - Treatment of hyperfunctional lines that result from the contraction of the underlying facial musculature with temporary flaccid paralysis of the injected muscles
 - BTX blocks neurotransmitter release at peripheral cholinergic nerve terminals (Fig. 26-5)
 - 7 toxin serotypes (A–G) bind to different sites on the motor nerve terminal and within the motor neuron
 - Botulinum toxin type A and type B are commercially available; A is the most potent
 - Each toxin serotype is composed of three domains: binding, translocation, and enzymatic
 - Synaptosomal-associated protein (SNAP-25) cleaved by serotypes A and E
 - Vesicle-associated membrane protein (VAMP, Synaptobrevin) cleaved by serotypes B, D, F, and G
 - Syntaxin 1 cleaved by serotype C1
 - Each toxin is made of a light chain (LC) and a heavy chain (HC) linked by a disulfide bond
 - Heavy chain: allows transport of toxin into the cholinergic motor neuron
 - Light chain: a Zn^{2+} -containing endopeptidase that blocks acetylcholine-containing vesicles from fusing with the terminal membrane of the motor neuron (SNARE complex)
 - SNARE (synaptosomal-associated protein receptor) proteins are presynaptic proteins involved in exocytosis of acetylcholine
 - Measured as 1 standard unit (median lethal intraperitoneal dose in mice (LD50) – amount injected necessary to kill 50% of Swiss-Webster mice)
- Commercially available BTX are listed in Table 26-18
- Events following Botox injection
 - Botox requires 24 to 72 hours to start to take effect; full effect by 2 weeks

TABLE 26-16 Correlation of Frost to Depth of Penetration

Level	0	1	2
Clinical appearance	No frost	Irregular light frost	Uniform white frost with pink showing through
Depth of penetration	Stratum corneum	Superficial epidermis	Full thickness epidermis

From Rubin MG. Trichloroacetic acid peels. In *Manual of Chemical Peels: Superficial and Medium Depth*. Philadelphia: J.B. Lippincott Company, 1995. Pp. 110–129

TABLE 26-17 Microdermabrasion Versus Dermabrasion

Procedure	Microdermabrasion	Dermabrasion
Mechanism of action	Produces a superficial ablation, primarily in the epidermis	Manual abrasion, wound healing by second intention allows re-epithelialization to occur from the underlying adnexal structures Depth of procedure: operator-dependent process and depends on coarseness of the dermabrading tip (fraise), number of brush strokes, pressure exerted on the electric handpiece, and tissue contact time
Indications	Superficial skin conditions Early photoaging, fine lines, and superficial scarring Effective microdermabrasion usually requires a series of 5–12 treatments	Lesions or defects of epidermis, papillary dermis, and upper reticular dermis Tattoos, rhinophyma, acne scarring, actinic keratoses, solar elastosis, and discoloration of photoaging 6–8 weeks following incision or injury (except when certain surgical procedures that involve extensive undermining, such as face lifts or brow lifts, to allow reestablishment of the underlying vascular bed. Wait at least 6 months)
Instruments	Components common to all systems Pump: generates a high-pressure stream of aluminum oxide or salt crystals Connecting tube and handpiece: delivers the crystals to the skin Vacuum: removes the crystals and exfoliated skin Crystals are discarded after use Eye protection from stray crystals	Abrasive wire or diamond wheel Rotational speeds of 12,000 to 15,000 rpm High-speed rotary motors are used to drive an abrading end piece
Contraindications	Active herpes infection Malignant skin tumors Evolving dermatoses Certain keratoses	History of hypertrophic scarring Isotretinoin within 6 to 12 months Active herpetic infection Malignant skin tumors Evolving dermatoses Certain keratoses
Complications	Rare; only mild postinflammatory hyperpigmentation Ocular complications (ie. corneal abrasion) – use eye protection Low risk, rapid recovery	Milia formation and a flare-up of acne Transient postoperative hyperpigmentation Postoperative viral infections Hypertrophic scarring

Data from Kunachak S, Leelaudomlapi P, Wongwaisayawan S. Dermabrasion: A curative treatment for melasma. *Aesth Plast Surg* 2001;25(2):114–117 and Freedman BM, Rueda-Pedraza E, Waddell SP. The epidermal and dermal changes associated with microdermabrasion. *Dermatol Surg* 2001;27(12):1031–1033.

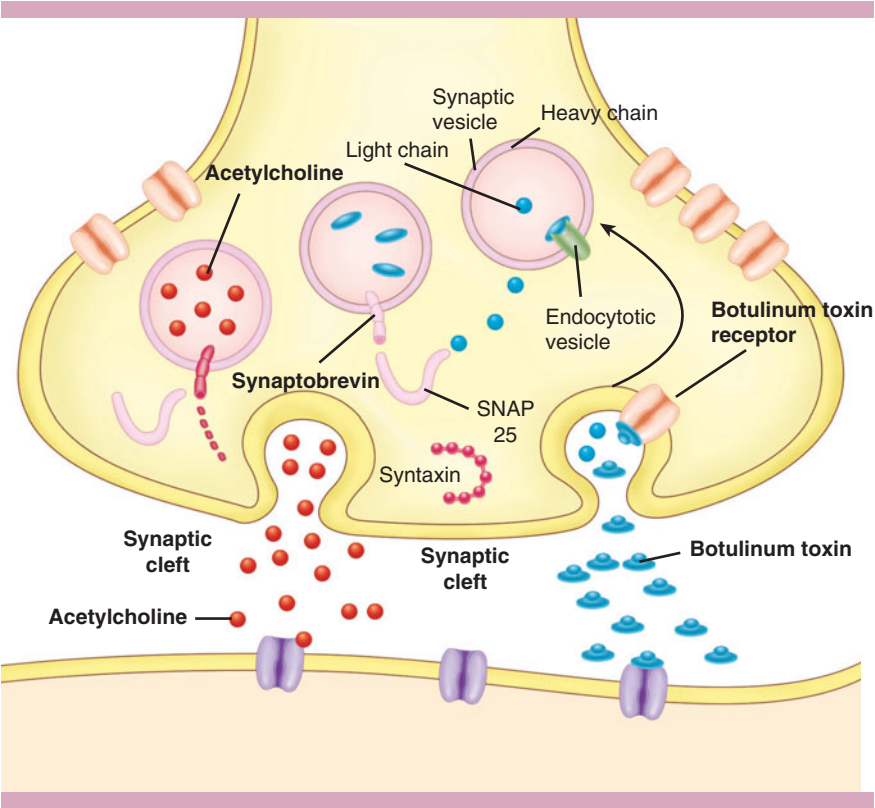


FIGURE 26-5 Botox mechanism of action. (Reprinted with permission from Baumann, L: *Cosmetic Dermatology: Principles and Practice, 2nd Ed.*, New York: McGraw-Hill; 2009.)

TABLE 26-18 Commercially Available BTX

Product	Botox (Allergan, Inc., Irvine, CA)	Dysport (Ipsen, Slough, U.K.)	Myobloc (Elan Pharmaceuticals, Sandiego, CA)
Serotype	• BTX type A	• BTX type A (abobotulinum toxin A)	• BTX type B
FDA (Food and Drug Administration)	• FDA approved in 1989 for treatment of strabismus and blepharospasm • FDA approved in 2000 for treatment of cervical dystonia • FDA approved in 2002 for treatment of glabellar rhytides, and hyperhidrosis • Currently available in the United States	• FDA approved in 2009 for treatment of glabellar lines and cervical dystonia	• FDA approved in 2000 for treatment of cervical dystonia. • Off-label treatment for facial wrinkles and hyperhidrosis. Currently available in United states • Available in Europe under the name Neurobloc
Packaging	• Comes in a vial containing 100 units	• Comes in a vial containing 500 units	• Available in vials containing 2500, 5000, and 10,000 units
Storage	• Must be stored frozen and then refrigerated when reconstituted	• Can be stored at room temperature	• Does not require constitution and is ready to use at pH 5.6 • Can be diluted to desired concentration

- Lasts approximately 3 to 5 months
- Muscle function returns as new neuromuscular junctions form (axonal sprouting)
- Antibodies to Botox
 - Antibody may develop to the binding site on the heavy chain of the BTX molecule
 - Prevents BTX binding to its receptor and thereby cripples the actions of the BTX
 - Increased risk of antibody formation at doses of more than 300 units at a time
 - Myobloc binding domain distinct from Botox (i.e., antibodies that neutralize BTX A would not neutralize BTX B, and vice versa)
- Uses for Botox on the face and neck
 - Numerous injection sites and concentrations published in literature
 - Glabellar rhytides are the only FDA-approved use of Botox for wrinkles
 - Injections under the guidance of electromyography (EMG) monitoring can be performed
- Glabellar furrows
 - Muscles involved (Fig. 26-6)
 - Procerus: brow depressor
 - Corrugator: brow depressor
 - Orbicularis oculi (medial fibers)
- Complications
 - Eyelid ptosis may develop when BTX affects the levator palpebrae superioris muscle, which normally elevates the eyelid



FIGURE 26-6 Muscles of the face treated by Botox. (Reprinted with permission from Baumann, L: *Cosmetic Dermatology: Principles and Practice*, 2nd Ed., New York: McGraw-Hill; 2009.)

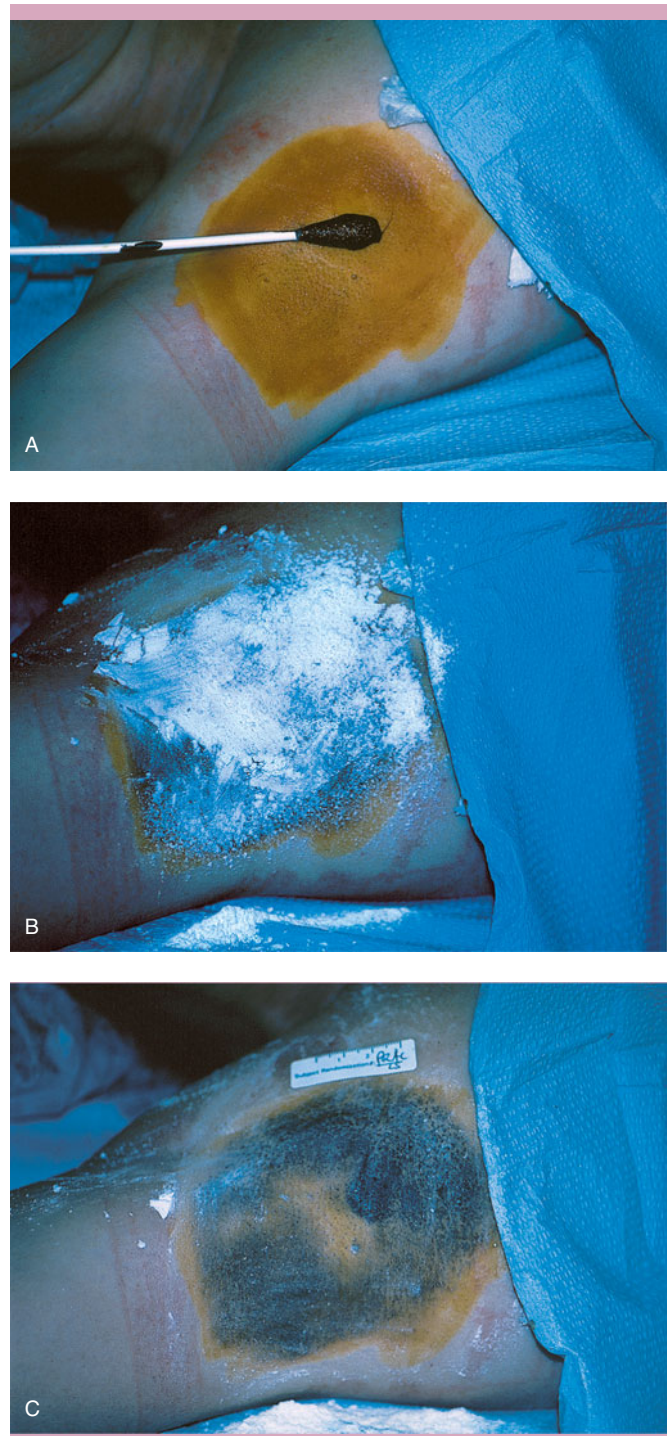


FIGURE 26-7 Iodine starch test for evaluation of hyperhidrosis. A. An iodine solution is applied to the affected area. B. Potato starch is then sprinkled over the area. C. The starch turns black in reaction to sweat, clearly delineating affected areas.

- May persist for 2 to 4 weeks
- Risk of eyelid ptosis is minimized by the correct injection volume and site of injection
 - Stay 1 cm above the orbital ridge
 - Have the patient stay vertical for 4 hours
 - Avoid manipulating injection site
- Aproclonidine 0.5% eye drops (Iopidine) one to three drops three times a day to the affected side
- Results in 1 to 2 mm of elevation
- Botox Treatment of Hyperhidrosis
 - Innervation of the eccrine glands: sympathetic nerves that use acetylcholine as the neurotransmitter
 - Botulinum toxin can temporarily reduce or even abolish sweat production
 - 50 units of Botulinum toxin injected into each axilla
 - Long-term satisfactory median responses lasting 6 to 19 months depending on dose and location
 - Extent of hyperhidrosis: evaluated by performing an iodine starch test of axillae, palms, or soles (Fig. 26-7)
- Contraindications to use of Botox
 - History of a neuromuscular disease (Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or myasthenia gravis)
 - Known history of sensitivity to Botox or human albumin
 - Aminoglycosides can interfere with neuromuscular transmission

- Pregnancy
- Lactation
- Age younger than 12 years

SOFT-TISSUE AUGMENTATION

- Injectable fillers are generally considered soft tissue augmentation materials
- Temporary injectable fillers are the most commonly used soft tissue augmentation products
- Used for wrinkles, scars, and augmentation of the lips and other tissues (Tables 26-19–26-22)

SCLEROTHERAPY

- When performing sclerotherapy, skin should be taut to facilitate cannulating the vessel
- Stretching the skin in opposite directions perpendicular to the vessel
- Compression should be applied to the injected site immediately post injection (Table 26-23)

ACNE SCAR TREATMENT

- Acne scarring classification and treatment options are described in Table 26-24

TABLE 26-19 Overview of Common Injectable Fillers

Filler	Type	FDA approved Indications	Treatment Techniques	Duration	Complication and Potential Adverse Reactions
Fat transfer	Autologous filler	N/A	Inject into subcutaneous fat layer and/or muscle Overcorrection is necessary	N/A	Prolonged edema, bruising, under-/overcorrection, migration, clumping, irregularities, fat necrosis, and infection
Fat autograft muscle injection (FAMI)	Autologous filler	N/A	Require nerve block if treated on face. Inject into muscle and immediate surrounding planes	Permanent or long lasting	Rare, including swelling, bruising, infection, scarring, and dyspigmentation
Autologen cultured human fibroblasts	Autologous filler	Sitmulates cutaneous collagen formation	Overcorrect by at least 20–30% Nerve blocks, local or topical anesthesia are needed Require a minimum of three injections over several weeks Skin testing not required	3–6 months	No risk for disease transmission or allergic reaction
AlloDerm	Cadaver-derived implant	Lip augmentation	Make tiny incision at both corners of lips Pass instrument from one incision to the other to make a tunnel Pass implant along the tunnel	From 6–12 months to several years	Overcorrection
Cymetra (acellular allogeneic dermis)	Cadaver-derived implant	Rhytides, nasolabial folds, and lips	Inject at midreticular level Double allergy testing is recommended	3–6 months	Bruising, redness, swelling, and wrinkling of skin
Human cadaver tissue (injectable, microparticulate acellular allogenic dermis)	Cadaver-derived implant	N/A	N/A	Lasts longer than bovine collagen	N/A

(Continued)

TABLE 26-19 (Continued)

Filler	Type	FDA approved Indications	Treatment Techniques	Duration	Complication and Potential Adverse Reactions
Human cadaver tissue (fascian lyophilized human particulate fascia lata)	Cadaver-derived implant	Stimulation of cutaneous collagen formation	N/A	3–6 months	Edema, erythema, and ecchymosis, inflammatory hyperpigmentation.
Zyderm (bovine dermal collagen dispersed in phosphate-buffered physiological saline containing 3% lidocaine)	Temporary filler	Facial rhytides, scars, and lip augmentation	Inject intradermally Infiltrate into superficial papillary dermis Require second skin test on contralateral arm Overcorrection is mandatory	3–6 months	Allergic reaction
Zyplast (bovine collagen cross-linked with glutaraldehyde and suspended in saline and 3 mg/ml lidocaine)	Temporary filler	Facial rhytides, scars, and lip augmentation	Place into midreticular or deep reticular dermis at dermal subcutaneous interface Require second skin test on contralateral arm Overcorrection is mandatory	3–6 months	Allergic reaction
CosmoDerm (human-based collagen insulated from human fibroblast cell cultures)	Temporary filler	Rhytides and scars (superficial skin defects)	Require pretreating with topical anesthetic cream Allergy test is not required	3–6 months	Mild swelling, erythema, bruising, and rarely, palpable lumps
CosmoPlast (human-based collagen cross-linked with glutaraldehyde)	Temporary filler	Rhytides and scars (reserved for deeper lines)	Require pretreating with topical anesthetic cream Allergy test is not required	3–6 months	Mild swelling, erythema, bruising, and rarely, palpable lumps
Restylane (hyaluronic acid derived from bacterial biofermentation process)	Temporary filler	Perlane 20 mg/mL: nasolabial folds and lips (fullness and pouting)	Should not be overcorrected Linear threading Serial puncture Fanning Cross-hatching	3–6 months	Redness, swelling, localized granulomatous reactions, bacterial infection, acneiform and cystic reaction, hypersensitivity

(Continued)

TABLE 26-19 (Continued)

Filler	Type	FDA approved Indications	Treatment Techniques	Duration	Complication and Potential Adverse Reactions
		Restylane 20 mg/mL: rhytides at glabellar, oral commissures and lip fullness, pouting, and vermillion border Restylane fine line 20 mg/mL: thin superficial lines, worry lines, periorbital and perioral lines			
Juvederm (viscoelastic, nonanimal hyaluronic acid gel)	Temporary filler	18 mg/g: superficial dermis, fine lines and rhytides 24 mg/g: mid dermis, deeper rhytides 30 mg/g: mid to deep dermis, deeper furrows, nasolabial fold, lip and cheek augmentation (not available in U.S.)	Correct placement in deep dermal and/ or deep dermal subcutaneous plane	3–6 months	Redness, swelling, localized granulomatous reactions, bacterial infection, acneiform and cystic reaction, hypersensitivity
Hylaform (viscoelastic hyaluronic acid gel from rooster combs)	Temporary filler	Cosmetic use	Correct placement in deep dermal and/ or deep dermal subcutaneous plane	2–3 months	Delayed inflammatory skin reactions
Sculptra (new-fill poly-L-lactic acid)	Temporary filler	Absorbable suture material and treatment of HIV-associated lipoatrophy	Correct placement in deep dermal and/ or deep dermal subcutaneous plane	12–18 weeks	Infection, allergic reaction, and inflammatory granulomas

(Continued)

TABLE 26-19 (Continued)

Filler	Type	FDA approved Indications	Treatment Techniques	Duration	Complication and Potential Adverse Reactions
Radiesse (radiance synthetic calcium hydroxyapatite microspheres suspended in polysaccharide gel)	Semi-permanent filler	Vocal cord augmentation and urinary incontinence	Inject into subdermis Intradermal placement can result in swelling, pain, persistent erythema, and visible or palpable granules. Slight over-correction is recommended Repeat injections 1-3 months after initial treatment Skin testing is mandatory	9-12 months	Pruritus or hypertrophic scarring, allergic reaction, granulomas (can be treated with corticosteroid injections)
Artecoll/Artefill (polymethyl-methacrylate microspheres in denatured bovine collagen)	Permanent filler	Pending for correction of facial rhytides, scars, and lip augmentation	Inject into the junction of dermis and subcutaneous space using tunneling technique Use small needle Overcorrection is not recommended Repeat treatment every 6 weeks until adequate augmentation Allergy test is required	Long lasting	Inflammation, induration, discoloration, ulceration, migration, and formation of granulomas
Silskin, AdatoSil 5000, Silikon 1000, Silicone oil	Permanent filler	Ocular medical purpose (not approved for cosmetic use)	Microdroplets of silicone oil are dispersed within dermal tissues, and fibrosis around these droplets localizes the material and provide "bulk" No allergy testing is required	Long lasting	Risks of infection, generally due to granuloma formation as the silicone becomes encapsulated as a foreign body in a chronic inflammatory reaction

(Continued)

TABLE 26-19 (Continued)

Filler	Type	FDA approved Indications	Treatment Techniques	Duration	Complication and Potential Adverse Reactions
UltraSoft, SoftForm (expanded polytetrafluoroethylene)	Implant	Subdermal soft tissue augmentation SoftForm: lip border, smile lines, naso labial fold, and frown lines UltraSoft: cheek and temple	Under local anesthesia Insert subdermally via 14- to 160-gauge angiocatheter	Long lasting	Higher rate of infection than permanent injectable microimplants
Gore-Tex (dual-porosity expanded polytetrafluoroethylene)	Implant	Vascular grafts, implant material, and soft tissue repair	Under local anesthesia Insert subdermally via 14- to 160-gauge angiocatheter	Long lasting	Transient bruising and swelling to infection of implant site, formation of fistula, and implant extrusion
Advanta facial implant (dual-porosity expanded)	Implant	Fill deep wrinkles or folds or to enhance, augment, or repair soft tissues of facial areas, such as lips	Require local anesthesia	Long lasting	Low incidence of complications

TABLE 26-20 Filler Contraindications

Common Contraindications
<p>Insotretinoin for 6 months prior or following treatment because it may increase chance of keloid-like scarring</p> <p>Collagen/scarring/connective tissue disorders</p> <p>Lupus for patients seeking bovine or porcine collagen. Other products may cause flare-ups as well</p> <p>Active diseases may affect outcome or increase risks</p> <p>Diabetes may affect outcome or increase risks</p> <p>Coagulation problems</p> <p>Excessive oral plaque or dental abscesses</p> <p>Herpes labialis</p> <p>Pregnant or lactating women</p> <p>Psychological conditions</p>

TABLE 26-21 Specific Product Contraindications

Product Name	Precautions/Contraindications
Zyderm/Zyplast (bovine dermal collagen)	<p>Adverse reaction to allergy test</p> <p>Presence of severe allergies manifested by history of anaphylaxis or multiple severe allergies</p> <p>Lidocaine hypersensitivity</p> <p>History of allergies to any bovine collagen product</p> <p>Contraindicated for use in the glabellar region</p>
Cymetra (injectable microparticulate acellular allogenic dermis)	<p>Autoimmune connective tissue disease</p> <p>Infected or nonvascular surgical sites</p> <p>Patients sensitized to specific antibiotics used in the manufacture of this preparation</p> <p>Periocular line correction or glabellar contouring</p>
CosmoPlast/CosmoDerm (human-based collagen cross-linked with glutaraldehyde)	<p>Severe allergies manifested by history of anaphylaxis</p> <p>Lidocaine hypersensitivity</p> <p>Contraindicated for use in glabellar region, breast augmentation, and implantation into bone, tendon, ligament, or muscle</p>
Juvederm (viscoelastic, nonanimal hyaluronic acid)	<p>Autoimmune disease</p> <p>Pregnancy</p> <p>Lactation</p> <p>Allergies to hyaluronic acid</p> <p>Direct sunlight or intense heat on treatment area for several days post injection</p>
Hylaform (hyaluronic acid)	Poultry allergy

TABLE 26-22 Fillers Injection Techniques

Injection Techniques	Fillers	Defects	Placement Level	Details
Kneading	Collagen	Superficial defects	Papillary dermis	<p>Shallow injection with needle inserted almost parallel to the skin</p> <p>The bevel of needle should be controlled with regard to its angle in relation to the skin surface</p> <p>A small bleb and blanching of the skin is seen with correct placement</p> <p>Gentle massage after injection to ensure the even distribution</p>
Piercing	Collagen	Moderate sized defects	Mid dermis	<p>Piercing the skin with needle at angle of 30 to 45 degree</p> <p>A bleb will not be produced but blanching may be seen</p>
	Hyaluronic acid	Deep defects	Deep dermis/ dermosubcutaneous junction/ subcutaneous fat	<p>May need multiple injections</p> <p>The needle should enter the skin at 45 to 90 degree angle</p>
Threading or tunneling	Hyaluronic acid / poly-l-lactic acid/calcium hydroxyapatite	Defects in a skin fold	Deep dermis/ dermosubcutaneous junction/ subcutaneous fat	<p>Single injection</p> <p>The needle pierces the skin once and is advanced parallel to the overlying defect</p> <p>The fillers can be delivered as the needle is inserted or withdrawn</p>
Serial puncture	Hyaluronic acid / poly-l-lactic acid/calcium hydroxyapatite	Defects in a skin fold	Deep dermis/ dermosubcutaneous junction/ subcutaneous fat	<p>Multiple injections</p> <p>The skin is held taut as the product is delivered in multiple small boluses over the entire length of the defect</p>
Fanning	Hyaluronic acid / poly-l-lactic acid/calcium hydroxyapatite/ autologous fat	Wide defects such as scars and areas of atrophy	Deep dermis/ dermosubcutaneous junction/ subcutaneous fat	<p>The needle insertion site remains the same with multiple threading injections extended across the defect in a “fan” shape</p>

TABLE 26-23 Sclerosing Agents

Agents	FDA Approval	Advantages	Disadvantages	Vein Diameter (mm)	Recommended Concentrations	Recommended Maximum Quantity Injected per Treatment Session
Osmotic Agents						
Hypertonic saline (18%)	Approved abortifacient	Lack of allergenicity	Damage to cellular tissues, produce ulcerations, necrosis, hyper-pigmentation, pain, muscle cramping	0.4–0.5 0.6–2	11.7% 23.4%	N/A
Hypertonic glucose/saline (Sclerodex)	Not approved	Minimized pain, less muscle cramping	Superficial necrosis, allergic reaction, hyper-pigmentation, mild pain	0.4–0.5 0.6–2	N/A	10 ml (1 mL per injection site, with 5 cm between each site)
Chemical irritants						
Chromated glycerine (Scleromo)	Not approved	Rare post-treatment hyper-pigmentation, necrosis, and bruising, even if injected extra-vascularly	Weak agent, therefore requires more treatment sessions, high viscosity, pain	< 0.4	50% 100%	N/A
Polyiodinated iodine (Variglobin, Sclerodine)	Not approved	Direct destruction of the endothelium	Necrosis, pain	0.4–0.5 0.6–2 3–5 > 5	0.1% 1% 2% 3–12%	3 mL of a 6% solution
Detergent sclerosing solutions						
Sodium morrhuate	Approved	N/A	Extremely caustic, necrosis, allergic reaction, anaphylaxis, pain	0.4–0.5 0.6–2 3–5	1% 2.5% 5%	N/A

(Continued)

TABLE 26-23 Sclerosing Agents (Continued)

Agents	FDA Approval	Advantages	Disadvantages	Vein Diameter (mm)	Recommended Concentrations	Recommended Maximum Quantity Injected per Treatment Session
Ethanolamine oleate (Ethamolin)	Not approved	Decreased risk of allergic reaction	Allergic reaction, pain	0.4–0.5 0.6–2	2 % 5 %	< 12 mL
Sodium tetradecyl sulfate	Approved	N/A	Epidermal necrosis, allergic reaction, hyperpigmentation, pain	0.4–0.5 0.6–2 3–5 > 5	0.1 % 0.25 % 0.5–1 % 2–3 %	4 mL of a 3 % solution by British manufacturers, and 10 ml of a 3 % solution by U.S. and Canadian manufacturers
Polidocanol (Aethoxy-sklerol)	Pending	Will not produce ulcerations, necrosis and allergic reaction are very rare, less hyperpigmentation and painless	Rare necrosis and allergic reaction	0.4–0.5 0.6–2 3–5 > 5	0.25–0.5 % 0.75 % 1–2 % 3–5 %	10 mL of a 6 % solution

TABLE 26-24 Acne Scarring Classification and Treatment Options

Grade	Level of disease	Examples of scars	Characteristics	Treatment options
1	Macular	Erythematous, hyper- or hypopigmented flat marks	Erythematous, hyper- or hypopigmented flat marks visible to patient or observer at any distance	Time, optimized home skin care, light strength peels, microdermabrasion, vascular or pigmented lasers, or intense pulsed light (IPL)
2	Mild	Mild rolling, small soft papular	Mild atrophy or hypertrophy that may not be obvious at social distances of 50 cm or greater and may be covered adequately by makeup or the normal shadow of shaved beard hair in men or normal body hair (if extrafacial)	Nonablative lasers, blood transfer, skin needling or rolling, microdermabrasion, dermal fillers
3	Moderate	More significant rolling, shallow boxcar, mild to moderate hypertrophic or popular scars	Moderate atrophic or hypertrophic scarring that is obvious at social distances of 50 cm or greater and is not covered easily by makeup or the normal shadow of shaved beard hair in men or body hair (if extrafacial), but is still able to be flattened by manual stretching of the skin (if atrophic)	Ablative lasers, dermabrasion, medical skin rolling, fractionated resurfacing, dermal fillers, subcision and blood transfer (if local), intralesional corticosteroids or fluorouracil and/or vascular laser (if hypertrophic)
4	Severe	Punched out atrophic (deep boxcar), ice pick, bridges and tunnels, marked atrophy, dystrophic significant hypertrophy or keloid	Severe atrophic or hypertrophic scarring that is obvious at social distances greater than 50 cm and is not covered easily by makeup or the normal shadow of shaved beard hair in men or body hair (if extrafacial) and is not able to be flattened by manual stretching of the skin	Punch techniques (float, excision grafting), focal trichloroacetic acid (CROSS technique) with or without resurfacing techniques (including fractionated resurfacing), fat transfer, occasionally rhytidectomy (if grossly atrophic), intralesional corticosteroids or fluorouracil and/or vascular laser (if hypertrophic)

QUIZ

Questions

- What shortens with age?
 - Ribosome
 - Nucleolus
 - Endoplasmic reticulum
 - Telomere
 - Golgi
- Which of the following is the shortest visible wavelength?
 - X-ray
 - Infrared
 - Gamma rays
 - Radio waves
- Which wavelength is within UV-A II?
 - 360 nm
 - 330 nm
 - 380 nm
 - 311 nm
 - 300 nm
- What is the unit of measurement for irradiance?
 - Joules/second
 - Watts
 - Watts/cm²
 - Joules/cm²
 - Nanometer
- Uniform white frost with pink showing through correlates with what depth of injury after a trichloroacetic acid peel?
 - Stratum corneum
 - Superficial epidermis
 - Full thickness epidermis
 - Papillary dermis
 - Reticular dermis
- What neurotransmitter is blocked by botulinum toxin?
 - Epinephrine
 - dopamine
 - Norepinephrine
 - Gamma aminobutyric acid
 - Acetylcholine
- What does Botox cleave?
 - Synaptosomal-associated protein
 - Vesicle-associated protein
 - Syntaxin
 - Cholinergic receptor
 - Acetylcholine
- Which of the following is NOT a contraindication for use of Botox cosmetic?
 - History of a neuromuscular disease (Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or myasthenia gravis)
 - Age younger than 18 years
 - Known history of sensitivity to Botox
 - Known sensitivity to human albumin
 - Pregnancy, lactation
- Which filler is contraindicated in a patient with poultry allergy?
 - Zyderm
 - Zplasty
 - Hylaform
 - Restylane
 - Evolve
- Which sclerosing agent is FDA approved for use in sclerotherapy?
 - Hypertonic saline
 - Hypertonic glucose
 - Sodium morrhuate
 - Polyiodinated iodine
 - Polidocanol

Answers

- D. Telomere. Telomeres are tandem repeats of the DNA base sequence (TTAGGGG) (T-thymine, G = guanine, A = adenosine), at the end of mammalian chromosomes. Telomere extension occurs by the action of telomerase; however, the DNA polymerase does not copy the final bases on each chromosome, resulting in telomere shortening after each round of cell division (i.e., aging). When the telomeres become too short, the cell will no longer divide.
- D. Gamma rays. Electromagnetic spectrum organizes radiation by energy. Photon energy is inversely proportional to wavelength (i.e., the shorter the wavelength, the higher the energy). From shortest to longest wavelength: gamma rays, x-ray, ultraviolet, visible, infrared, microwave, radio wave.
- B. 330 nm. Ultraviolet radiation is divided into UV-A I (400 to 340 nm), UV-A II (340 to 320 nm), UVB (320 to 290 nm). UV-A, a longer wavelength, causes delayed tanning and reaches deeper into the papillary dermis. UV-B causes acute sunburn and is predominantly absorbed by the epidermis.
- C. Watt/cm². Irradiance is measured in watts/cm². Other laser characteristics include: wavelength (nanometer), spot size (millimeter), pulse duration (seconds), fluence (joules/cm²), power (joules/second).

5. C. Full thickness epidermis. After defatting the skin, chemical peeling agents are applied to the skin. Skin keratin begins to agglutinate. Depth of peel can be correlated with the intensity of the frost: no frost (stratum corneum), irregular light frost (superficial epidermis), and uniform white frost with pink showing through (full thickness epidermis).
6. E. Acetylcholine. Neurotransmitters are chemicals used to signal between a neuron and another cell. They are present in the presynaptic element, bind to post-synaptic receptors, and must be in sufficient quantity to affect the post-synaptic cell. Botulinum toxin blocks neurotransmitter release at peripheral cholinergic nerve terminals. Epinephrine, dopamine, norepinephrine, gamma aminobutyric acid, melatonin, serotonin and glutamic acid are other neurotransmitters.
7. A. Synaptosomal-associated protein. Seven botulinum toxin serotypes (A–G) bind to different sites on the motor nerve terminal and within the motor neuron. Botox is botulinum toxin type A, and Myobloc is botulinum toxin type B. Synaptosomal-associated protein (SNAP-25) is cleaved by serotypes A and E. Vesicle-associated membrane protein (VAMP, Synaptobrevin) is cleaved by serotypes B, D, F, and G. Syntaxin 1 is cleaved by serotype C1. Cleavage of these proteins prevents exocytosis of acetylcholine into the synapse between the motor neuron and the skeletal muscle cell.
8. B. Age under 18 years. Contraindications for use of Botox include: history of a neuromuscular disease (Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or myasthenia gravis); known history of sensitivity to Botox or human albumin; aminoglycoside use which can interfere with neuromuscular transmission; pregnancy; lactation; and age younger than 12 years of age.
9. C. Hylaform. Fillers are derived from various sources and should be avoided if patients are allergic to components within each filler. For instance, Zyderm and Zyplast are derived from bovine dermal collagen, Restylane is derived from non-animal hyaluronic acid gel, Evolence from porcine collagen, and Hylaform from rooster combs.
10. C. Sodium morrhuate. Only sodium morrhuate and sodium tetradecyl sulfate are FDA approved for use in sclerotherapy. All others are not approved. Hypertonic saline is FDA approved as an abortifacient.

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IMMUNOLOGY REVIEW

KURT LU
GENEVIEVE WALLACE

THE IMMUNE RESPONSE (FIG. 27-1)

- The human body can respond to antigen via innate and/or adaptive immunity
- Innate immunity (nonspecific, nonclonal, no anamnestic characteristics)
 - Characteristics
 - Immediate first line defense against pathogens composed of three major components
 - ▲ Nonspecific physical and chemical barriers
 - ▲ Recruitment and activation of leukocytes
 - ▲ Release and/or activation of extracellular humoral mediators (i.e., cytokines, complement)
 - Exists prior to exposure to a given microbe or antigen (requires no previous exposure) and is rapidly available on pathogen encounter (minutes)
 - Key components
 - Physical and chemical barriers to pathogen invasion:
 - ▲ Skin, mucous membranes, cilia, and secretions (mucous and sweat) cover body surfaces and prevent microorganisms and other potentially injurious agents from entering the tissues beneath
 - △ Mucous traps, dissolves, and sweeps away foreign substances
 - △ Sweat contains lactic acid and other substances that maintain the surface of the epidermis at an acidic pH, thereby decreasing colonization by bacteria and other organisms
 - ▲ Chemical barrier antimicrobial substances include enzymes that can directly injure or kill microbial pathogens

Complement

- Alternate pathway of complement can be spontaneously activated by microbial surfaces in the absence of specific antibodies

Antimicrobial Peptides

- Produced by keratinocytes; include cathelicidins and B-defensins
 - Defensins (alpha or beta) and cathelicidins have multiple receptor-mediated effects on the immune cells
 - Defensins are secreted by resident epithelial cells or by transient leukocytes that coat and destabilize the cell membrane of pathogens
 - β -Defensins interact with chemokine receptor 6 (CCR6) which results in attraction of dendritic cells and memory T cells
 - Defensins may facilitate microbial antigen delivery to dendritic cells
 - Cathelicidins are secreted by neutrophils, keratinocytes, epithelial cells, mast cells, and monocytes-macrophages

Pattern Recognition Receptors (PRR)

- Phagocytic cell PRRs recognize highly conserved pathogen amino acid sequences and result in a variety of signals
 - Examples of PRRs:
 - *Toll-like receptors* (TLRs): mediate innate immune response in host defenses; expressed in peripheral blood leukocytes (monocytes, B cells, T cells, granulocytes, and dendritic cells. Modulate inflammatory responses via cytokine release. Activation of TLRs can lead to tissue injury (e.g., TLR2 activation by *Propionibacterium acnes* induces inflammatory responses in acne which result in tissue injury)

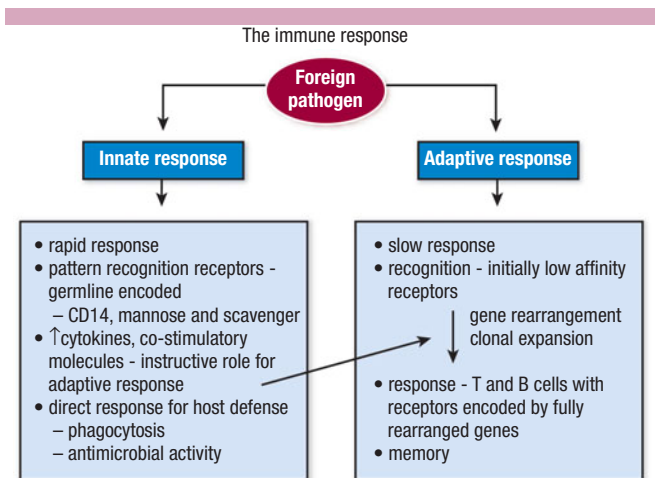


FIGURE 27-1 The immune response. (Reprinted with permission from Wolff, K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- Innate transmembrane receptors that recognize different types of pathogen-associated molecular patterns (PAMPs), which are molecular patterns unique to pathogens
- Ligands include lipopolysaccharide, peptidoglycan, CpG DNA
- Humans have at least 10 different TLRs
- TLRs identify the nature of the pathogen and result in NF κ B activation, which results in appropriate cytokine and chemokine expression, along with increased expression of additional immune system receptors
- Triggering receptors expressed on myeloid cells (TREM): amplify innate immune responses

CELLS OF THE INNATE IMMUNE SYSTEM

• Phagocytes

- Integral to the innate immune response and are composed of macrophages and polymorphonuclear cells; activity is sometimes regulated by TLR's and complement receptors
- Phagocytes can also be activated by cells of the adaptive immune system: CD4⁺ cells can activate macrophages to produce TNF- α , IL-1, IL-12, interferon- γ and nitric oxide
- Phagocytic cells (macrophage, neutrophils) recognize pathogens via cell-surface pattern recognition receptors (PRRs)
- Macrophage mannose receptor: only on macrophages, recognizes certain sugar molecules

found on bacteria and some viruses (HIV), direct phagocytic receptor (transmembrane bound)

- Scavenger receptors: recognize anionic polymers and also acetylated low-density lipoproteins, involved in the removal of old red blood cells and pathogens
- **Natural killer (NK) cells**
 - Large granular lymphocyte: ~2% of the circulating lymphocytes. Kill pathogens within infected cells through perforin/granzyme- or Fas/FasL-dependent mechanisms or indirectly through cytokine secretion activated by IFN- γ , IFN- β , and macrophage-derived cytokines (TNF- α , IL-12)
 - Reside in blood, spleen, lung, liver, GI tract, and uterine deciduas
 - Main function is to provide cytotoxic activity toward virally infected cells and neoplastic cells—both antibody-independent and -dependent pathways exist
 - Respond early to microbial assault and interact with other cells of the innate immune system; able to nonspecifically kill target cells without prior sensitization
 - While they express neither a T-cell receptor nor a B-cell receptor, NK cells demonstrate specificity in their ability to recognize targets
 - NK cells recognize killer inhibitory receptors on MHC class I molecules which results in a negative signal to the NK cell. The NK cell recognizes the cell as self and does not kill the cell
 - Express distinct surface molecules
 - CD16 is a receptor for the Fc portion of Ig (used in antibody-dependent cellular cytotoxicity)
 - CD56 is a neural adhesion molecule that can bind to CD56 on other cells
 - Activated by IL-2, IL-7, IL-12, and IL-18
 - NK cells express the beta chain of the IL-2 receptor; therefore, resting NK cells can respond directly to IL-2
 - Capable of producing cytokines following activation, such as IFN- γ and TNF- α , which can affect the proliferation and differentiation of other cell types
 - Mechanisms of cytotoxicity
 - NK cells lyse targets through calcium-dependent release of preformed granules that contain perforin and granzysin
 - ▲ Perforin, like complement, intercalates into the target cell membrane, forming pores
 - ▲ Granzysin is a cationic protein that can induce apoptosis by initiating DNA fragmentation; may potentiate the activity of perforin in the lysis of target cells

- Receptor-induced apoptosis
 - ▲ Activated NK cells will induce apoptosis or lysis of target cells expressing certain receptors such as FAS and TRAIL ligands death receptor-4 and death receptor-5
 - ▲ NK cells are also capable of killing specifically when they are provided with an antibody [antibody-dependent cellular cytotoxicity (ADCC)]; ADCC occurs via binding of the antibody to the Fcγ receptor (CD16) located on the NK cell, leading to apoptosis of the target cell
 - ▲ NK cell killing activity can be regulated by interaction with MHC-I on the target cell via called the killer cell inhibitory receptor (KIR)
 - ▲ Dendritic cells are stimulated to move from the periphery to the lymph node by TNF-α, where they mature from phagocytes into nonphagocytic efficient antigen-presenting cells
- **Eosinophils**
 - Develop and mature from CD34 + hematopoietic progenitor cells and are released into the circulation as mature cells
 - Bilobed nucleus
 - IL-5 (released by T_H2 cells) increases the production of mast cells in the bone marrow
 - Possess chemokine receptors that, when bound, activate, degranulate, and coordinate chemotaxis
 - Membrane bound core containing secondary granules which contain basic proteins
 - *Four basic proteins*: major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil peroxidase (EPO), eosinophil derived neurotoxin (EDN)
 - *Primary granules*: lack a core and have variable sizes; contain Charcot-Leyden crystal protein (galectin-10)
 - Cyclooxygenase and 5- and 15-lipoxygenase which are required to synthesize prostaglandins and leukotrienes
 - *Activation of eosinophils*: various mediators activate eosinophils: cytokines (TNF alpha, GM-CSF, IL-3 and IL-5), complement components (C3a and C5a), lipid mediators (LTC4 and PAF), chemokines and IgA and IgG Fc receptors. CC chemokine subfamily (CCL5, CCL7, CCL11, CCL14 and CCL240) bind to the chemokine receptor CCR3
 - Eosinophil activating cytokines IL-3, IL-5 and GM-CSF enhance cell survival, eosinophil maturation, chemotactic responses, and leukotriene production
 - *Types of eosinophil activation*: expression of P selectin on endothelial surface, induction by non specific activators such as IL-1 and TNF alpha, induction by IL-4 and IL-13
 - After cytokine and chemokine activation, the high affinity IgE receptors (FcεRI) are expressed along with an increase in complement receptors
 - Degranulation releases major basic protein, which causes degranulation of mast cells and basophils
- **Basophils**
 - Growth factors include IL3, IL-5, and GM-CSF
 - TGF-β IL3 suppress eosinophil differentiation and promote basophil differentiation
 - Eotaxins attract and degranulate (release histamine and IL-4)
 - Pathogens coated with fragments of the complement protein C3 bind strongly to B cells
- **Keratinocytes**
 - Can activate an immune and/or inflammatory response through secretion of cytokines, arachadonic acid metabolites, complement components, and antimicrobial peptides
 - Following appropriate stimuli the following cytokine response may occur:
 - Initiation of inflammation: IL-1, TNF-alpha, IL-6
 - Modulation of langerhan cells: IL-1, GM-CSF, TNF-alpha, IL-10, IL-15
 - ▲ T cell activation: IL-15, IL-18
 - ▲ T cell inhibition: IL-10, TGF-beta
 - ▲ Th1 response: IL-12, IL-18, Th2 response: thymic stromal lymphopoietin or Th17: IL-23
 - Bridging innate immunity to adaptive immunity
 - Macrophages and dendritic cells present antigens to T cells
 - Interaction of PAMPs and TLRs on the surface of dendritic cells triggers secretion of innate immune cytokines (INF-α, INF-β, IL-12, TNF-α) and chemokines, which may affect both T and B cells

ADAPTIVE IMMUNITY

- An antigen-specific immune response resulting in the activation of humoral and cell-mediated immunity, mediated by specific antibodies
- T-lymphocytes and B-lymphocytes differentiate from a common lymphoid stem cell in the bone marrow
- **B-lymphocytes (B cells)**: antibody-producing cells
 - Represent 5% to 10% of the lymphocytes found in the blood
 - Express cell membrane immunoglobulin (Ig): majority expresses both IgM and IgD

- A small minority of B cells expresses surface IgG or IgA
- Possess a variety of receptors on their surface (complement receptors, class I and II MHC molecule receptors)
- Analogous to T cells, B cells have specific antigen receptors, which are immunoglobulins (Ig)
- On activation and cross-linking of surface Ig by specific antigen, B cells undergo proliferation and differentiation to produce plasma cells
- Plasma cells are nondividing, specialized cells whose only function is to secrete Ig
- Immunoglobulins (Igs) (Fig. 27-2)
 - Exquisite specificity for antigen is achieved by a mechanism of genetic recombination that is unique to Ig and T-cell receptor genes
 - The antigen-binding site consists of a highly variable sequence created by the juxtaposition

- of two constituent polypeptides: heavy (H) chain and one of two alternative light (L) chains, κ or λ
- These polypeptides can be divided into two segments: antigen-binding amino-terminal *variable domain* and one or more carboxy-terminal *constant (nonvariable)* domains that are generally responsible for biologic functions and activities of the molecules
- Ig antigen receptor
 - ▲ A virtually limitless array of specific-antigen receptors is possible
 - ▲ The great variability is accomplished by recombination of genomic segments that encode the variable portions of Ig
 - ▲ The products of these rearranged genes provide the B cell with its own unique receptor
 - ▲ The mature receptor consists of the products of two or three such rearranged segments
 - △ V (variable) and J (joining) for IgL (light) chains
 - △ V, D (diversity), and J for IgH (heavy) chains
 - ▲ DNA rearrangement
 - △ Controlled by recombinases
 - △ Sequential and carefully regulated process
 - △ Leads to translation of one receptor of unique specificity for any given B-lymphocyte
 - △ Unique specificity is achieved through a process termed *allelic exclusion* (only one member of a pair of allelic genes potentially contributing to an Ig is rearranged at a time)
 - ▲ Somatic hypermutation
 - △ A feature of the V-region construction that is unique to B cells
 - △ As antigen is introduced into the system, and mature B cells remain genetically responsive to the antigenic environment
 - △ As a result, a few B cells increase their affinity for the antigen
 - △ Higher-affinity B cells are preferentially activated at exposure to the antigen
 - △ As a result, the average affinity of antibodies produced during the course of an immune response increases (termed *affinity maturation*)

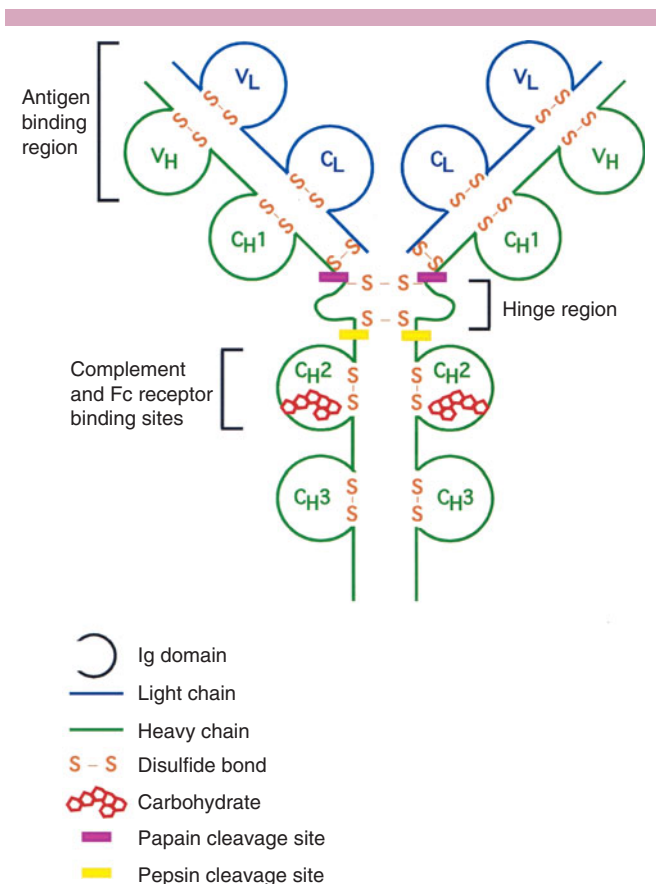


FIGURE 27-2 Immunoglobulin (Ig) molecule. (Reprinted with permission from Wolff, K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill, 2008.)

- Secretion of Ig molecules
 - ▲ The cell-surface antigen receptors can be secreted in large quantities as antibody molecules
 - ▲ The effector functions of antibodies can be carried out in solution or at the surface of other cells
 - ▲ Secretion is accomplished by alternative splicing of Ig transcripts to include or exclude a transmembrane segment of the Ig heavy chains
- Ig classes (isotypes) (Table 27-1)
 - ▲ Five major classes in order of abundance: IgG, IgM, IgA, IgD, and IgE
 - ▲ Determined by the sequence of the constant region of its heavy chain (Ch)
 - ▲ Isotype or class switching: B cell can change the class of antibody molecule that it synthesizes by using different Ch genes without changing its unique antibody specificity
- **T lymphocytes**
 - T-cell development: progenitor cells exit the bone marrow and undergo further maturation and selection in the thymus; they express antigen receptors needed for self/nonself discrimination (Fig. 27-3)
 - In the thymus: T cells rearrange their specific T-cell antigen receptors (TCRs) and then express CD3 along with the TCRs on their surface
 - The TCR for antigen is a heterodimeric membrane molecule expressed exclusively by T-lymphocytes
 - T cell subpopulations are based on surface expression of CD4 and CD8, as well as by their function in the immune response
 - *Helper T cells* (T_H cells): express CD4 surface molecules and recognize antigen bound to class II major histocompatibility complex (MHC) molecules
 - Play a central role in the initiation and regulation of immune responses through the secretion of cytokines and activation of macrophages
 - Important effectors of cell-mediated immunity
 - Essential contributors to the generation of chronic inflammatory responses
 - Cytotoxic activity either through the elaboration of cytotoxic cytokines (i.e., lymphotoxin, tumor necrosis factor α) or directly through interaction with antigen bound to MHC class II molecules
 - Function depends on the cytokine profile produced, which characterizes them as T_H type 1 (T_{H1}) or T_H type 2 (T_{H2})
 - Naïve CD4⁺ cells differentiate into immature effector T cells (T_{H0}). Depending on activation signals and the cytokine milieu in the micro-environment, T_{H0} can differentiate into several different classes of cells: (1) T_{H1} (2) T_{H2} , (3) T_{H17} (4) regulatory T cells, (5) natural killer T cells (see section above)
 - (1) T_{H1} cells produce primarily IFN- γ , IL-2, and tumor necrosis factor α (TNF- α); important in cell-mediated immunity to intracellular pathogens (i.e., tubercle bacillus)

TABLE 27-1 Classes of Immunoglobulin

Characteristic	IgG	IgA	IgM	IgD	IgE
Heavy chain	γ	α	μ	δ	ϵ
Light chain	κ, λ	κ, λ	κ, λ	κ, λ	κ, λ
J chain	—	+	+	—	—
Molecular weight	150,000	160,000–400,000	900,000	180,000	190,000
Serum half-life (days)	23	6	5	3	2
Serum concentration	1200	140–400	20–50	4	0.02
Complement fixation	+	\pm	+	—	—
Placental transfer	+	—	—	—	—

Used with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 5th ed. New York: McGraw-Hill, 1999, p. 380.

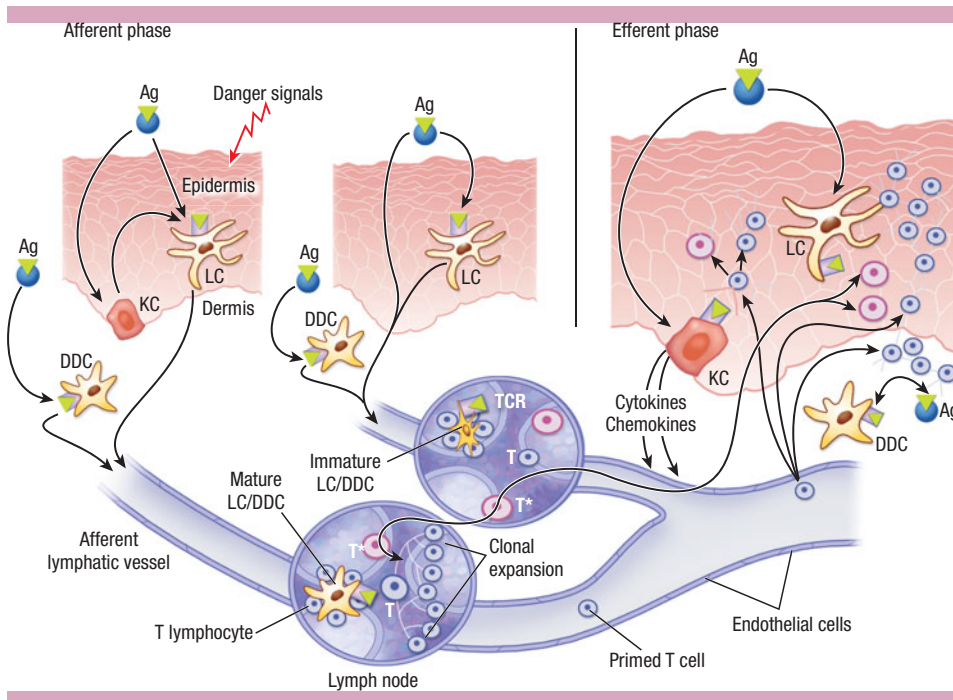


FIGURE 27-3 T-cell development. (Reprinted with permission from Wolff, K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- (2) T_H2 cells produce predominantly IL-4, IL-5, IL-6, IL-10, IL-13 and IL-15; predominate in immediate or allergic type I hypersensitivity
- (3) $Th17$: These cells are produced directly from naïve $CD4^+$ cells and produce IL-17
- (4) Regulatory T cells: (Treg cells):
 - ▲ Function as suppressors or downregulators of immune responses
 - ▲ Molecular basis of this activity is being defined. Several classes of regulatory T cells have been described
 - ▲ Naturally occurring circulating $CD4^+/CD25^{hi}$ are the best characterized population
 - △ The $CD4^+/CD25^{hi}$ regulatory T cells have been found to express FOXP3, a gene encoding a transcription factor important in the regulation of regulatory T cells
 - △ Mutation in FOXP3 in humans leads to a rare disease with regulatory cell dysfunction called IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked)
 - △ Mechanism of suppression is via direct contact with target cells
- Other regulatory T cell populations have been described and have been generated in vitro including:
 - $TH3$ cells which are $CD4^+$. Mechanism of suppression is via production of IL-TGF- β
 - $Tr1$ cells which are $CD4^+/CD25^{low}$
 - $CD8^+$ cells have also been described. Mechanism of suppression is via production of IL-10 and TGF- β
 - $CD28^-/CD8^+$ regulatory T cells. Mechanism of suppression is thought to be via direct cell contact and also via induction of regulatory receptors on other cells
 - Thought to involve the production of nonspecific inhibitory cytokines
- *Cytotoxic T cells* (Tc cells): cytotoxic effectors
- Cytotoxic $CD8^+$ T cells can further differentiate into Tc1 or Tc2 cells
 - Express CD8 surface molecules and recognize antigen bound to class I MHC molecules
 - Capable of direct killing of target cells expressing an appropriate viral peptide bound to a self-MHC class I molecule
 - Highly specific process that requires direct apposition of Tc cell and target cell membrane
 - Following killing, Tc cell is capable of detaching from target and seeking another target cell
 - Destruction of target cells requires the insertion of perforins from the Tc cell into the target cell membrane that results in fragmentation of target cell nuclear DNA (apoptotic)

Cell-Mediated and Humoral Immune Response

- Antibodies, dissolved in blood, lymph, and other body fluids, bind the antigen and trigger a response to the antigen (i.e., release cytokines)

- **T-cell response**

- Viruses and intracellular parasite antigens are processed into peptides within antigen-presenting cells (APCs) and are bound to the heavy chain of an MHC class I and presented to a CD8 + (cytotoxic) T cell
- If a specific antigen encounters its specific T-cell receptor, IL-2 is released, and T-cell activation, along with expansion of the antigen-specific cytotoxic T-cell (Tc) line, follows
- If an antigen-specific Tc cell encounters a cell expressing its specific antigen, the activation signal that ensues results in exocytosis of granzymes (granules containing enzymes), perforins, cytolyticins, lymphotoxins, and serine esterases, which kill the APC
- Extracellular antigens
 - Taken up by APCs by pinocytosis and then processed into peptides
 - Peptides are presented in the context of an MHC class II molecule to a CD4 + T cell
- After activation, CD4 and CD8 cells may differentiate toward T_H1 or T_H2 cytokine profiles depending on cytokine milieu
 - *T_H1 cell activation*
 - Goal: macrophage activation and increased cell-mediated immunity
 - T_H1 cytokine profile: IL-2, IFN- γ , TNF- α , and IL-12
 - ▲ IL-2: T- and B-cell activation
 - ▲ IFN- γ : activator of macrophages and NK cells
 - ▲ TNF- α : activates macrophages and stimulates the acute-phase response along with IL-1
 - ▲ IL-12 activates CD8 + (Tc) cell proliferation
 - ▲ Antigen binding to receptors results in release lytic agents (perforins, cytolyticins, lymphotoxins)
 - *T_H2 cell activation*
 - Goal: B-cell activation
 - IL-2 production by T_H1 cells induces the CD4 + T_H2 cells to transform, differentiate, and divide
 - T_H2 cytokine profile: IL-4, IL-5, IL-10, and IL-13
 - ▲ IL-4: promotes the synthesis of antibodies by stimulating B-cell differentiation
 - ▲ Downregulates IFN- γ ; therefore, can suppress cell-mediated immunity
 - ▲ Can cause production of IgE
 - ▲ IL-5: helps with B-cell differentiation
 - ▲ Facilitates IgA synthesis
 - ▲ Stimulates growth of eosinophils
 - ▲ IL-4, IL-10, and IL-13 can inhibit T_H1 cell release of IFN- γ and IL-2; thus capable of suppressing cell-mediated immunity

- Antibody-dependent cellular cytotoxic (ADCC) reactions
 - Target cell is linked to the T cell by an antibody bridge
 - Fab portion of the antibody binds to a specific membrane antigen on the target cell
 - Fc portion of the antibody binds to the Fc receptor on the T cell
- **B-cell response**
 - Like T cells, B cells contain membrane bound IgM antibody specific for the antigen epitope
 - Primary immune response: initial encounter
 - Antigen bound to the APC receptor along with cytokines IL-2 and IL-4 (stimuli for T cells) triggers the antigen-specific B cell to differentiate and divide
 - IgM is secreted initially, and subsequent gene arrangements result in a switch to IgG, IgA, and IgE
 - B memory cells of all classes are generated and migrate to various lymphoid tissues, where they have extended survival
 - Plasma cell: B cell that secretes antibodies
 - Secondary immune response: subsequent exposure to the same antigen
 - Activation of antigen-specific B cell results in more efficient antibody synthesis and faster isotype switching from IgM to IgG
 - A greater amount of IgG with higher affinity for the antigen during subsequent encounters
 - Predominance of IgA secretion in mucosal tissues

Myeloid Progenitor Cell

- Dendritic cells express costimulatory molecules and cytokines in response to pathogen antigens
 - Proteoglycans first recognized by PRRs
 - Then costimulatory molecules and cytokines are upregulated via toll-like receptor-2

Langerhans Cells and Other Dendritic Cells

- Bone marrow derived leukocytes that can migrate and present antigen
- *Langerhans cells* (LC) are found in all stratified squamous epithelia
- The following molecules are expressed by LCs:
 - Langerin (CD 207): calcium dependent lectin; helps identify LC cells, CD1a, MHC class II antigens: HLA-DR, HLA-DP, HLA-DQ; and CD 39
 - Birbeck granules: pentilaminar cytoplasmic structures that appear as a tennis racket shape with electron microscopy
 - LC are activated under inflammatory conditions. LC express chemokine receptors CCR2 and CCR6 (their ligands are secreted by endothelial cells and keratinocytes)

- *Dendritic leukocytes* (DDC) are found in the dermis
 - Express the following molecules: CD1b and CD1c and factor XIIIa, MHC class II molecules DEC205/CD205
- DDCs enter the skin secondary to CCR2-dependent cell migration; other dendritic cells also migrate to the skin (plasmacytoid DCs and inflammatory dendritic epidermal cells)
- Dendritic cells: stimulate antigen specific responses in naïve, resting T cells. (T cells are not able to recognize soluble protein antigen)
- CD1 dependent antigen presentation: CD1 family expressed by LCs and DDCs
- Antigens presented to T cells bound to MHC class II molecules are recognized by CD4 cells, while antigens bound to MHC class I are recognized by CD8 + cells
- Second signals: MHC-peptide complexes provide the first signal to T cells, but this first signal is insufficient for the full activation of naïve T cells, co-stimulatory molecules deliver second signals which are induced by surface receptors triggered by ligands secreted by other somatic cells or by microbial products
- Examples of co-stimulatory molecules and their ligands:
 - ICAM-1 binds to LFA-1 and LFA-3 (ligand of T cell expressed CD2), CD24/CD24L, CD40/CD40L, CD70/CD70L, receptor activator of nuclear factor KB (RANK)/RANKL

CYTOKINES

- Polypeptides serve as intercellular messengers in order to mediate immune responses
 - Autocrine in nature: affect the cell that releases the cytokine
 - Paracrine in nature: affect the adjacent cells
 - Endocrine in nature: affect distant cells
- Produced by inflammatory cells (lymphocytes, monocytes) as well as resident cells in the skin (keratinocytes, Langerhans cells, and endothelial cells)
- Variable effects: see Table 27-2 on specific cytokines, their actions, and major sources of the cytokines
- Involved in innate immunity (occurs without the activation of B or T cells) or adaptive immunity (depends on a B or T cell reacting to a specific antigen)
- Primary cytokines: can initiate all events required to bring about leukocyte infiltration in tissues (i.e., IL-1 and tumor necrosis factor), can be viewed as part of the innate immune system

- Secondary cytokines: induced after stimulation by IL-1 and/or TNF family molecules Th17: IL-17
- Jak/STAT pathway: common cell surface to nucleus pathway used by the majority of cytokines. Jaks (Janus family kinases) are upregulated after stimulation of cytokine receptors (such as IFN gamma), Jak kinases phosphorylate STATs (signal transducers and activators of transcription) through Src homology 2 (SH2) domains; STATs translocate to the nucleus and stimulate transcription of specific genes (Fig. 27-3)
- The IL-1 family share a common signaling domain with the TLRs: Toll/L-1 receptor (TLR) domain. When activated by TLR domain-containing proteins (i.e., MyD88), TLR will activate IL-1R-associated kinase (IRAK) and ultimately activation of nuclear factor KB (NF-KB), IL-1 accessory protein (RACp) and tumor necrosis factor receptor-associated factor (TRAF)
- Tumor necrosis factor alpha can trigger apoptosis and/or nuclear factor KB activation
- Medications that target cytokines include receptor fusion proteins (etanercept), monoclonal antibodies (infliximab and adalimumab), and receptor antagonists that neutralize or inhibit various cytokines

CHEMOKINES

- Class of cytokines that express both chemoattractant and cytokinetic properties
 - Leukocytes can respond to a panel of different chemokines
 - Neutrophils are recruited first, while monocytes and immature dendritic cells are recruited later
- Structures contain a four-cysteine motif with a disulfide bond between cysteines 1,3 and 2,4 along with an N-terminus critical for receptor recognition and activation
- Four subfamilies, based on the position of the first two of four conserved cysteines (α , β , γ , and κ)
- Multiple cell types can produce the same chemokine, and a cell can produce many different chemokines in response to a single stimulus
- Chemokine receptors
 - Members of the large family of G protein-coupled receptors possessing seven transmembrane-spanning domains
 - One receptor is capable of binding to various chemokines
 - Binding of the ligand to the chemokine receptor induces conformational changes in the receptor and leads to activation of G proteins

TABLE 27-2 Cytokines of Particular Importance for Cutaneous Biology

Cytokine	Major Sources	Responsive Cells	Features of Interest	Clinical Relevance
IL-1 α	Epithelial cells	Infiltrating leukocytes	Activate from stored in keratinocytes	IL-1Ra used to treat rheumatoid arthritis
IL-1 β	Myeloid cells	Infiltrating leukocytes	Caspase 1 cleavage required for activation	IL-1Ra used to treat rheumatoid arthritis
IL-2	Activated T cells	Activated T cells, Treg cells	Autocrine facto for activated T cells	IL-2 fusion toxin targets CTCL
IL-4	Activated Th2 cells, NKT cells	Lymphocytes, endothelial cells, keratinocytes	Causes B-cell class switching and Th2 differentiation	—
IL-5	Activated Th2 cells, mast cells	B cells, eosinophils	Regulates eosinophil response to parasites	Anti-IL-5 depletes eosinophils
IL-6	Activated myeloid cells, fibroblasts, endothelial cells	B cells, myeloid cells, hepatocytes	Triggers acute-phase response, promotes immunoglobulin synthesis	—
IL-10	T cells, NK cells	Myeloid and lymphoid cells	Inhibits innate and acquired immune response	—
IL-12	Activated APCs	Th1 cells	Promotes Th1 differentiation, share p40 subunit with IL-23	Anti-p40 inhibits Crohn disease and psoriasis
IL-13	Activated Th2 cells	Monocytes, keratinocytes, endothelial cells	Mediates tissue response to parasites	—
IL-17	Activated Th17 cells	Multiple cell types	Mediates autoimmune diseases	Potential drug target in autoimmune disease
IL-23	Activated dendritic cells	Memory T cells, Th17 cells	Directs Th17 differentiation, mediates autoimmune disease	Anti-p40 inhibits Crohn disease and psoriasis
TNF- α	Activated myeloid, lymphoid, and epithelial cells	Infiltrating leukocytes	Mediated inflammation	Anti-TNF- α effective in psoriasis
IFN- α and IFN- β	Plasmacytoid dendritic cells	Most cell types	Major part of antiviral response	Elicited by topical imiquimod
IFN- γ	Activated Th1 cells, CD8 T cells, NK cells, dendritic cells	Macrophages, dendritic cells, naive T cells	Macrophage activation, specific isotype switching	IFN- γ used to treat chronic granulomatous disease

APC = antigen-presenting cell; CTCL = cutaneous T-cell lymphoma; IFN = interferon; IL = interleukin; NK = natural killer; NKT = natural killer T cell; Th = T helper; TMF = tumor necrosis facto; Treg = T regulatory.

- The G protein causes exchange of GDP for GTP and begins a chain of events resulting in intracellular signaling responses
- Biologic effects of chemokines
 - Influences leukocyte trafficking at all stages of maturation
 - Regulates cells trafficking within primary and secondary lymphoid organs (i.e., from bone marrow to the spleen, lymph node, or thymus)
 - Controls the type of inflammatory infiltrate at a site of inflammation
 - Regulates the expression and activity of adhesion molecules on the leukocyte surface to increase the adhesion of leukocytes to activated endothelium
 - Recruitment and activation of neutrophils and mononuclear cells to sites of inflammation
 - Regulates proliferation of subsets of mature stem cells and immature progenitor cells
- Secretion of chemokines
 - Released by endothelial cells, leukocytes, and tissue cells at the sites of inflammation
 - Locally retained on cell surface proteoglycans, establishing a chemokine chemical gradient that begins at the endothelium surface and increases as the cell approaches the focus of inflammation
 - Thought to be upregulated in inflammatory foci and certain inflammatory diseases (i.e., glomerulonephritis, rheumatoid arthritis, ulcerative colitis, and Crohn disease)
- Cyclooxygenase (COX) pathway
 - Key enzyme in the pathway, cyclooxygenase (COX), has two different isoforms
 - COX-1: constitutively expressed in cells and associated with cellular homeostasis
 - COX-2: requires specific induction, upregulated in inflammatory conditions, and associated with synthesis of proinflammatory prostaglandins
 - COX-1 and COX-2 are inhibited by nonsteroidal anti-inflammatory drugs
 - Derivatives of the cyclooxygenase pathway
 - Prostaglandins (PGs)
 - ▲ *PGD2*
 - △ Released by activated mast cells
 - △ Generated very rapidly after IgE-dependent activation
 - △ Enhances venular permeability
 - △ Promotes leukocyte adherence to vascular endothelial cells
 - △ Coronary and pulmonary vasoconstrictor
 - △ Peripheral vasodilator
 - △ Potent inhibitor of platelet aggregation
 - △ Chemokinetic for neutrophils and in conjunction with LTD4 can induce the accumulation of neutrophils in the skin
 - △ Important hypotensive effects, particularly in mastocytosis, suggesting that it is probably an important contributor to the anaphylactic response
 - △ Metabolite of PGD2 is elevated in patients with systemic mastocytosis
 - ▲ *PGE2*
 - △ Proinflammatory effects
 - △ Released in response to infection with ameba (specifically *Entamoeba histolytica*) and parasites
 - △ Released by endothelial cells following trauma, leading to tissue inflammation
 - △ Plays an important role in the secondary immunosuppression following surgical stress
 - △ Synthesized by the synovial lining in rheumatoid arthritis
 - ▲ *PGI2 and PGE2*
 - △ Potent vasodilators
 - △ Enhance capillary permeability and edema formation
 - Derivatives of lipoxygenase (LO) pathway
 - *Thromboxanes/thromboxane A2*

EICOSANOIDS

- Large, complex family of immunomodulatory and vasoactive compounds derived from arachadonic acid (AA) generated by mast cells, basophils, eosinophils, and mononuclear leukocytes
- General
 - Peroxidation of AA by phospholipases generates prostaglandins (via the cyclooxygenase [COX] pathway) or thromboxanes and leukotrienes (via the lipoxygenase [LO] pathway)
 - Play a key role in inflammatory and anaphylactoid responses
- Arachadonic acid
 - Polyunsaturated fatty acid with 20 carbon atoms and four double bonds
 - Resides in cell membrane lipids
 - Derived from dietary sources or synthesized by desaturation and elongation of linoleic acid

- Promotes platelet aggregation, bronchoconstriction, and vasoconstriction
- Contributes to the pulmonary hypertension and acute tubular necrosis that occurs in shock
- Predominately found in platelets and monocytes
- *Leukotrienes*
 - Mediate wheal and flare reactions, edema formation, and bronchial constriction
 - Combined with histamine can result in hypotension
 - One of the major inflammatory mediators involved in asthma pathogenesis
 - Enhances airway hyperresponsiveness and smooth muscle hypertrophy
 - Causes mucus hypersecretion and mucosal edema
 - Induces influx of eosinophils into the airway tissue key players in anaphylactic reactions and IgE-mediated syndromes
 - Mediators of the vascular sequelae of anaphylaxis as well as of shock states resulting from sepsis or tissue injury
 - LTB₄
 - Predominantly formed and released by neutrophils
 - Neutrophil chemoattractant
 - LTC₄
 - Derived from activated mast cells, basophils, and eosinophils
 - Potent vasodilator

COMPLEMENT

- General
 - Group of plasma and cell membrane proteins that play a role in inflammation, tissue injury, hemostasis, and immune response to antigens
 - Some of the proteins exists as precursor (inactive) enzymes that are cleaved by proteolysis; products then act as a catalyst for the next step in the cascade
 - The central step of the complement pathway is the generation of C3b cleavage by C3 convertases and subsequent assembly of C5b-9, the membrane attack complex (MAC)
- Main functions
 - Lysis of cells
 - Generate inflammatory mediators and chemotactic fragments
 - Opsonization for enhanced phagocytosis
- Three pathways for complement activation
 - Classical pathway
 - Activated primarily by antibody-antigen complexes
 - Also activated by oligosaccharides, porins from gram-negative bacteria, ligand-bound C-reactive protein
 - The starting point of the classical pathway is C1
 - Steps of classical pathway (Fig. 27-4)
 - ▲ Aggregation of IgG or IgM activates C1
 - ▲ C1 is a calcium-dependent complex of three subunits: C1q, C1r, and C1s
 - ▲ Activated C1 then cleaves C4 to C4a and C4b
 - ▲ C4a is a weak anaphylatoxin
 - ▲ C4b binds C2 in the presence of Mg²⁺
 - ▲ C1 cleaves the attached C2 into C2b and C2a
 - ▲ C2b is released, cleaved by plasmin, and has kinin-like activity
 - ▲ C2a stays bound to C4 to form C4b2a—the classical pathway C3 convertase that generates C3
 - Alternative pathway
 - Activation usually occurs independent of antibody
 - May be activated by bacterial surfaces, virus-infected cells, certain viruses, abnormal erythrocytes, and lymphoblastoid cell lines
 - The starting point of the alternative pathway is C3b
 - Steps of the alternative pathway (Fig. 27-5)
 - ▲ Starts with internal hydrolysis of C3 on interaction with water to form C3 (H₂O)
 - ▲ C3 (H₂O) then binds factor B and magnesium
 - ▲ Factor D then cleaves the bound factor B into Ba and Bb
 - ▲ Ba is released
 - ▲ Bb stays bound to C3(H₂O) to form C3 (H₂O), which is the initial C3 convertase of the alternative pathway that cleaves C3
 - ▲ C3 is cleaved to C3a and C3b
 - ▲ C3a is released and becomes a potent anaphylatoxin
 - ▲ C3b binds factor B in the presence of magnesium, and factor B is cleaved by factor D into Bb and Ba
 - ▲ Ba is released
 - ▲ Bb stays bound to form C3bBb, the C3 convertase of the alternative pathway
 - Lectin pathway
 - C4 activation can be achieved without antibody and C1 participation
 - Pathway is initiated by three proteins: a mannan-binding lectin (MBL) [mannan-binding

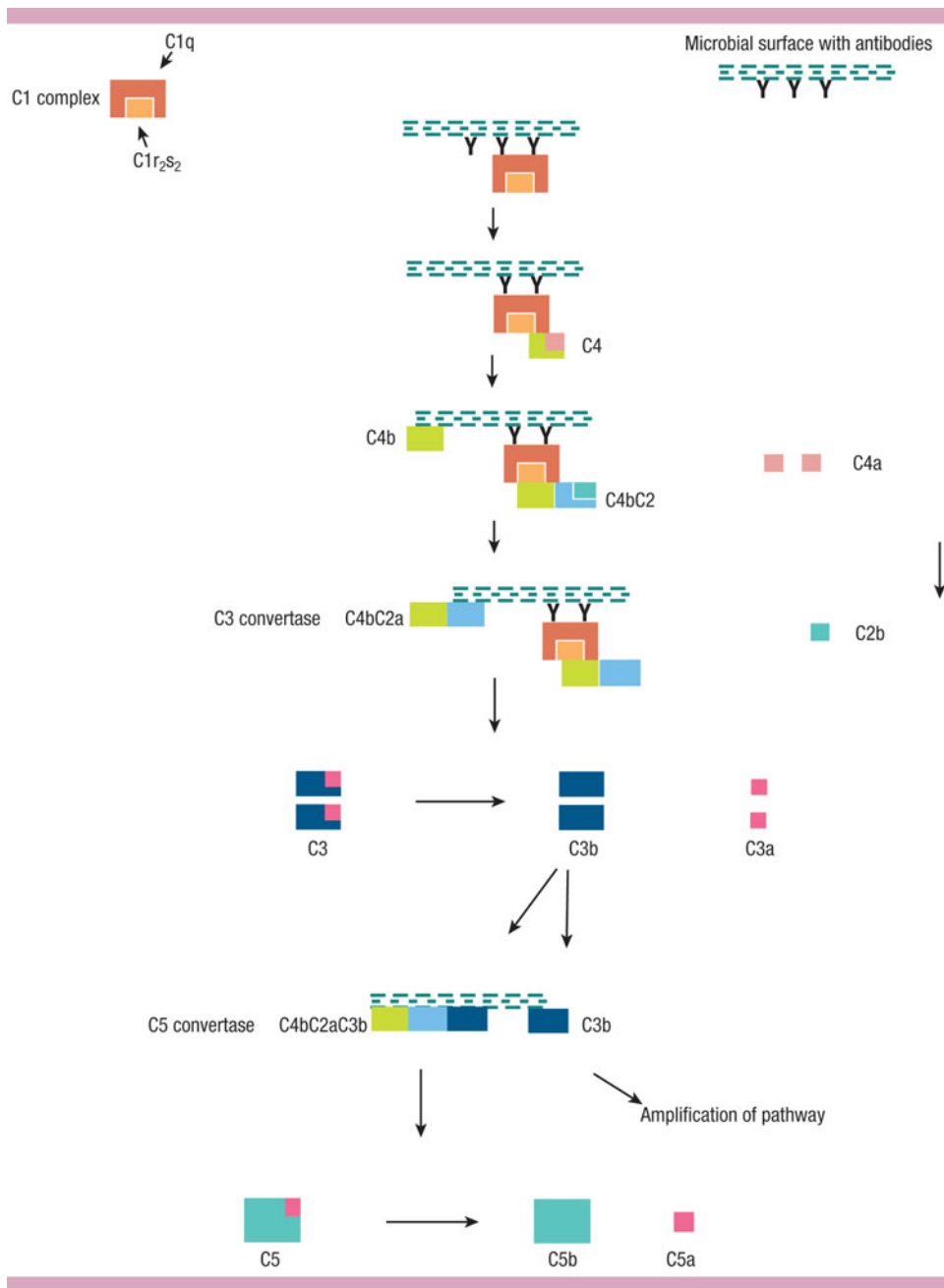


FIGURE 27-4 Classical pathway of complement activation. (Reprinted with permission from Wolff, K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

protein (MBP)], which interacts with two mannan-binding lectin-associated serine proteases (MASP and MADSP2), analogous to C1r and C1s

- This interaction generates a complex analogous to C1qrs and leads to antibody-independent activation of the classical pathway
- Common portion of pathway/membrane attack complex (Fig. 27-6)
 - At this point, the classical, alternative, and lectin pathways all have generated C3b using their respective C3 convertases, C4b2a, and C3bBb

- The two convertases assist in the cleavage of C3 to C3a (an anaphylatoxin) and C3b
- C3b binds to the next protein, C5
- C5 is also cleaved by the C3 convertases into C5a and C5b
- C5a is released and becomes the most potent anaphylatoxin
- C5b becomes the point of assembly for MAC (membrane attack complex)
- C5b associates with target cell membrane and C6
- C5b6 then associates with the assembly of C7, C8, and C9

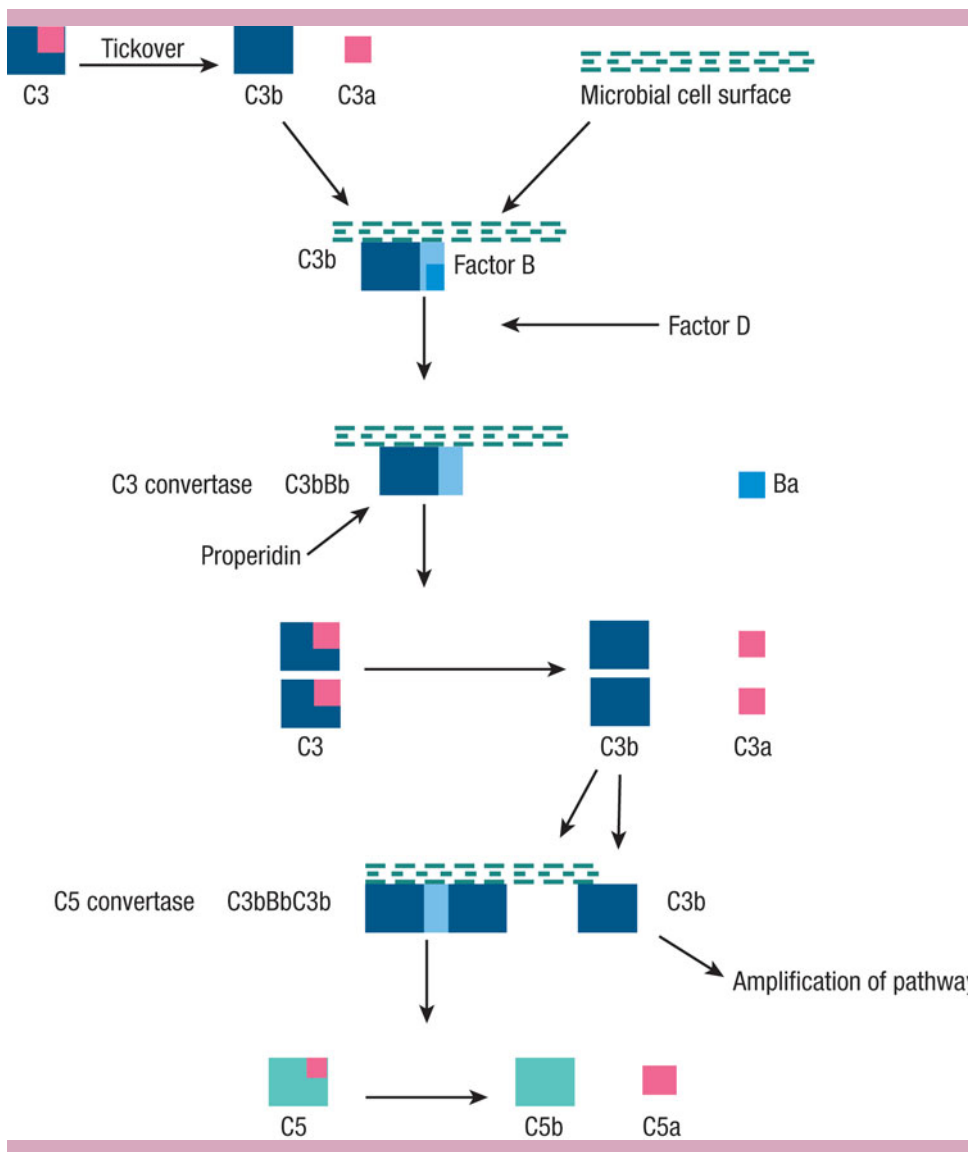


FIGURE 27-5 Alternate pathway of complement activation. (Reprinted with permission from Wolff, K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- C5b6789 is the MAC that forms transmembrane channels (holes) in the cell membrane that allow an influx of water and ions to cause cell swelling and lysis
- Points of regulation
 - Classical pathway
 - C1 is inhibited by C1 inhibitor (C1 INH)
 - C1 esterase inhibitor (C1 INH) deficiency causes angioedema
 - Factor I inhibits formation of C3 convertase
 - C4-binding protein inhibits formation of C3 convertase
 - Decay accelerating factor (DAF) inhibits formation of C3 convertase
 - Alternative pathway
 - Factor H inhibits formation of C3 convertase
 - Factor P (properdin) protects C3 convertase
- Anaphylatoxins
 - C3a, C5a, C4a
 - Cause release of histamine from mast cells, degranulation of basophils, increase in vascular permeability
 - Anaphylatoxins are regulated by a carboxipeptidase present in plasma
- *Neutrophils*
 - Derived from a pluripotent hematopoietic stem cell
 - Myeloblasts develop into neutrophils, the stages are under the influence of granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF)
 - Cytoplasmic granules include lysozyme, myeloperoxidase, defensins

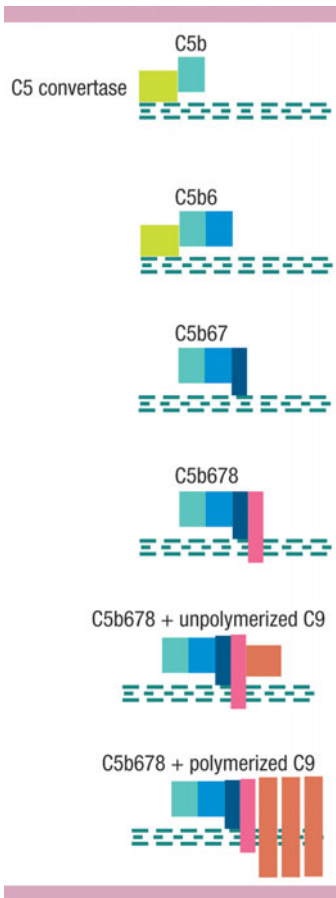


FIGURE 27-6
Formation of the membrane attack complex. (Reprinted with permission from Wolff, K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- Secondary granules include lactoferrin, collagenase, gelatinase, vitamin B12 binding protein, and complement receptor 3
- Granules fuse with incoming phagocytic vacuoles that contain ingested bacteria
- IL-8 is a potent chemoattractant and neutrophil activator, other chemoattractants include: N-formylmethionyl-leucyl-phenylalanine, complement factor 5a, leukotriene B₄, and platelet activating factor (PAF)
- Neutrophils adhere to sites along endothelium after recognizing sites of activation (e.g., chemokine expression) and traverse the endothelium to enter the tissue and fight infection
- Neutrophils produce cytokines that stimulate and attract other phagocytes and lymphocytes
- Mechanisms of killing may be oxygen dependent or independent
- *Mast cell*
 - Arise from CD34⁺, KIT⁺ pluripotent progenitor stem cell
 - Primary cell in immunoglobulin E-mediated inflammatory reactions

- Cytoplasmic granule content, size, and susceptibility to pharmacologic treatments vary with location of the cells
- All mast cells contain tryptase, histamine, proteoglycans (heparin and chondroitin sulfate E)
- Types of mast cells
 - TC mast cells (MCTC): contain tryptase and chymase, located in submucosal tissue
 - T mast cells (MCT): contain tryptase and lack chymase; increased in allergic and parasitic diseases, decreased in gastrointestinal mucosa in patients with human immunodeficiency virus
 - Chymase only mast cells: located in skin, lymph nodes, intestinal submucosa
- Mast cell activation and mediators: see Table 27-3
- Pre-formed secretory mediators are released in response to aggregation of the high-affinity IgE receptor
- Histamine and tryptase are released after activation of mast cells
- Histamine receptors: H₁ on epithelial cells, vascular and perivascular cells; H₂ on epithelial cells of the gastrointestinal tract, H₃ are found in the brain and gastrointestinal tract and may be associated with headache; H₄ expressed on bone marrow cells, eosinophils and mast cells

EXAMPLES OF IMMUNE-MEDIATED DERMATOLOGIC DISEASES

Hypersensitivity Reactions: Resulting From Humoral Immunity or Cell-Mediated Immunity

- *Type I reactions*: anaphylaxis reactions (IgE-mediated)
 - Immediate hypersensitivity reactions: symptoms begin within 30 minutes of the exposure
 - Clinical classification of Type I reactions:
 - *Local*: allergic rhinitis, allergic asthma, atopic (familial predisposed) dermatitis
 - *Systemic/anaphylaxis*: hypersensitive response in genetically susceptible individuals to small amounts of antigen to which they have been sensitized previously
 - Generalized vasodilation and increased vascular permeability can lead to hypotension, shock, and ultimately death
 - Early signs and symptoms include angioedema, urticaria, dyspnea, vomiting, and abdominal cramping
 - Common triggers are foods (peanuts, eggs, shellfish), drugs (aspirin, radiocontrast media, penicillin and other beta-lactam antibiotics), *Hymenoptera* venom, and pollens

TABLE 27-3 Selected Mast Cell Mediators

Mediators	Biologic Effects	Possible Consequences
Pre-formed		
Histamine	Vasodilation, increased vascular permeability, gastric hypersecretion, bronchoconstriction	Hypotension, flushing, urticaria, abdominal pain; (peptic, colic) diarrhea, malabsorption
Heparin	Anticoagulant, inhibition of platelet aggregation	Prolonged bleeding time
Tryptase	Endothelial cell activation, fibrinogen cleavage, mitogenic for smooth muscles cells	Osteoporosis/osteopenia, disruption of cascade systems (clotting, etc.)
Chymase	Converts angiotensin I to II, lipoprotein degradation	Hypertension
Newly Synthesized		
Leukotrienes	Increase vascular permeability, bronchoconstriction, vasoconstriction	Brochospasm, hypotension
Prostaglandins	Vasodilation, bronchoconstriction	Flushing, urticaria
Cytokines		
Stem cell factor	Growth and survival of mast cells, chemotaxis of KIT ⁺ cells	Mast cell hyperplasia, focal aggregates
Tumor necrosis factor- α	Activation of vascular endothelial cells, cachexia, fatigue	Weight loss, fatigue
Transforming growth factor- β	Enhanced production of connective tissue components	Fibrosis
IL-5	Eosinophil growth factor	Eosinophilia
IL-6	Growth and survival of mast cells	Fever, bone pain, osteoporosis/osteopenia
IL-16	Lymphocyte accumulation	Focal aggregates
Hypertension IL = interleukin.		

- Mechanism
 - Sensitization to a particular antigen occurs after an initial exposure by injection, ingestion, inhalation, or insect sting
 - IgE antibody is produced, which then binds to its receptor on the surface of mast cells and basophils
 - After reintroduction of antigen to the sensitized host, the antigen binds to several cell-bound IgE antibody molecules, resulting in cross-link and signal transduction
 - Mast cells degranulate and release histamine, leukotriene, serotonin, and bradykinin, resulting in vasodilation, increased vascular permeability, contraction of smooth muscle in bronchi, and increased secretions
 - Primary mediators include TNF- α , IL-1, IL-6, prostaglandins, leukotrienes, and histamine

- Treatment: epinephrine, diphenhydramine, aminophylline, and corticosteroids
 - *Type II reactions*: cell surface antigen-antibody cytotoxicity reactions (antibody-mediated)
 - Antibody is directed against an antigen that may be intrinsic (innately part of the host tissues) or extrinsic (absorbed onto host tissue surfaces during exposure)
 - IgG and IgM antibodies bound to these antigens form in situ complexes that activate the classical pathway of complement and generate mediators of acute inflammation at the site
 - Antibody-dependent cell-mediated cytotoxicity (ADCC): NK cells destroy antibody-coated target cells via perforins and serine proteases, which results in pore formation and cell lysis
 - In some cases, formation of the antigen-antibody complexes does not lead to activation of the complement system but still can lead to cell injury
 - Examples of cytotoxic reactions: transfusion reactions, reactions to certain drugs (penicillin, quinidine, methyl dopa), and autoimmune hemolytic anemia or thrombocytopenia
 - *Type III reactions*: antigen-antibody complex reactions
 - Circulating antibodies bind to antigen and form complexes that, in the presence of excess antigen, escape phagocytosis and deposit on the surface of blood vessels or tissues
 - Antigen-antibody complexes activate complement and release C5a that acts as a potent neutrophil chemotactic factor and anaphylatoxin; clotting factors are also activated
 - Neutrophils are attracted to the area of complex deposition and release lysosomal enzymes, causing tissue destruction
 - Examples of antigen-antibody complex reactions
 - *Arthus reaction*: local type III reaction usually seen when antigen is injected into the skin
 - ▲ An IgG antibody directed against the antigen forms immune complexes that bind Fc receptors on leukocytes and mast cells
 - ▲ The immune complexes also activate complement and release of chemotactic factors (C3a, C5a), leading to neutrophil infiltration and activation
 - *Serum sickness*: allergic vasculitis characterized by joint pain, fever, pruritic rash, and lymphadenopathy that leads to a complement-mediated systemic immune complex reaction
 - ▲ Occurs by the injection of foreign serum or its products into the blood
 - ▲ Antibody-antigen complexes activate the complement cascade and also trigger ligation of the FcγRIII mast cell receptor, resulting in histamine release
 - ▲ Associated medications include sulfonamides, penicillin, cephalosporins, phenytoin, thiourea, lamotrigine and streptokinase
 - *Type IV reactions*: delayed-type hypersensitivity (DTH) reactions
 - Consequence of cell-mediated immunity (antigen-specific T cells): appears in 24 to 48 hours
 - Three clinical examples of Type IV reactions:
 - *Delayed-type hypersensitivity*: antigen introduced by sting (venom) or iatrogenically (PPD)
 - *Contact hypersensitivity*: antigen in the form of haptens from a topical exposure (i.e., Rhus dermatitis, nickel)
 - *Gluten-sensitive enteropathy*: antigen introduced parenterally
- ### Vitiligo
- Clinical: depigmented patches of skin in various distributions on the body
 - Etiology: loss of melanocytes from the epidermis
 - Considered by most to be an autoimmune phenomenon
 - Both melanocyte autoantibodies and T cells are involved in the pathogenesis
 - CD4+/CD8+ ratio is reversed, with predominant CD8+ T cells suggesting a role of CD8+ mediated cytotoxicity to melanocytes in disease etiology
 - Associated with other autoimmune diseases as well as organ-specific autoantibodies: diabetes mellitus, pernicious anemia, systemic lupus erythematosus, thyroid disease (Graves' disease)
 - Treatment: steroids, immune modulators: calcineurin inhibitors, phototherapy, punch grafts
- ### Psoriasis
- Clinical: a systemic inflammatory disorder that manifests as sharply demarcated red plaques with silvery-white scales on the extensor surfaces and scalp
 - Types
 - *Plaque psoriasis*: raised lesions most common on the extensor surfaces of the knees, elbows, scalp, and trunk (Fig. 27-7)
 - *Guttate psoriasis*: droplike lesions; may follow streptococcal pharyngitis
 - *Inverse psoriasis*: flexural surfaces, intertriginous areas
 - *Pustular psoriasis*: diffuse erythema with pustular eruption can occur with fever
 - *Nail psoriasis*: nail pitting, oil spots, and onycholysis
 - *Scalp psoriasis*: erythema and silvery scale
 - *Erythrodermic psoriasis*: widespread inflammation and exfoliation; exacerbation of unstable plaque psoriasis



FIGURE 27-7 Psoriasis.
(Reprinted with permission
from Wolff, K et al. *Fitzpatrick's
Dermatology in General
Medicine*, 7th Ed. New York:
McGraw-Hill; 2008.)

- *Inflammatory progressive arthritis*: approximately 10% to 30% of patients; asymmetric oligoarthritis occurs in as many as 70% of patients with psoriatic arthritis
- Pathogenesis
 - T cells and macrophages can be detected in newly forming lesions
 - Activated memory T-lymphocytes release proinflammatory cytokines, which results in proliferation of keratinocytes and leukocyte recruitment
 - CD4⁺ and CD8⁺ T cells are both present in the dermal and epidermal infiltrate, respectively
 - T_H1 cytokines (IL-2, INF- γ , IL-6, IL-12, and TNF- α) are produced by the T cells, keratinocytes, and antigen-presenting cells
 - IL-23 is overproduced by dendritic cells and possibly keratinocytes in psoriatic lesions
- stimulates T_H17 cells to produce cytokines that stimulate keratinocytes proliferation
- T_H17 family of cytokines include IL-17A, IL-17 f, IL-21, IL-22, and TNF- α
- Elevated TNF- α levels lead to increased production of proinflammatory cytokines by T cells and macrophages
- Treatment: targets T cells or their cytokines
- Ultraviolet A (UV-A) light; etanercept, efalizumab, psoralen plus UV-A light (PUVA); UV-B light; Goeckerman regimen (coal tar followed by UV-B exposure); Ingram method, (anthralin cream is applied to the skin after a tar bath and UV-B treatment); oral retinoids; methotrexate; cyclosporine; alefacept; infliximab; etanercept, adalimumab, ustekinumab; topical steroids; topical calcipotriene; coal tar; topical tazarotene; laser treatment; and combinations of the preceding treatments; patients should avoid oral steroids owing to rebound effect

Alopecia Areata (AA)

- Clinical: an autoimmune nonscarring alopecia; usually localized; however, more severe forms may affect the entire scalp (alopecia totalis) or body (alopecia universalis)
- Pathogenesis
 - Associated with certain HLA alleles (HLA-DR4, -DR6, -B12, -B18, -B13, and -B27)
 - CLA⁺ CD4 and CD8 T-lymphocytes are thought to be involved in the pathogenesis
 - Associated autoimmune diseases: diabetes mellitus, systemic lupus erythematosus, Graves, and vitiligo

Sarcoid

- Clinical: a multisystemic disorder, unknown etiology, clinical manifestations include cutaneous lesions (25% of patients); are categorized as specific or non-specific based on the histologic presence or absence of noncaseating epithelioid granulomas, respectively; systemic involvement is seen in 70% of cutaneously involved patients
- The skin disease does not correlate with prognosis or extent of visceral involvement (except in erythema nodosum which is a self-limiting condition)
- Nonspecific lesions seen in sarcoidosis (biopsy does not show granulomas):
 - *Erythema nodosum* (EN): most common non-specific lesion; tender, erythematous nodules most commonly on legs; associated with a better prognosis
 - May be self-limited and asymptomatic; better prognosis
- Specific lesions (biopsy shows granulomatous inflammation)
 - *Lupus pernio* (Fig. 27-8): violaceous patches and plaques most commonly on the nose; more common in women and associated with pulmonary involvement; resolution with scarring is possible; marker for insidious disease; progresses over many months. The cheeks, ears, digits, and toes may be similarly affected. Complications include ulceration and involvement of underlying bone structures
 - Papules/plaques/nodules
 - Head and neck more common for papules
 - Legs: plaques; *angiolupoid sarcoid* (plaques with telangiectasias); marker for pulmonary fibrosis
 - *Subcutaneous nodules* (Darier-Roussy): firm, painless subcutaneous nodules that represent sarcoidosis; this subset is highly associated with systemic disease
 - Scar sarcoidosis (i.e., vaccination site, tattoos)



FIGURE 27-8 Lupus pernio. (Courtesy of Dr. Asra Ali.)

- Unique variants: ulcerative (legs), ichthyosiform lesions, scarring/nonscarring alopecia
- Syndromes
 - *Lofgren's syndrome*: hilar adenopathy, EN, fever, migrating polyarthritides, and acute iritis
 - *Heerfordt's-Waldenström syndrome* (*uveoparotid fever*): parotid gland enlargement, fever, cranial nerve palsy, anterior uveitis
- Systemic disease manifestations
 - Pulmonary
 - Interstitial lung disease may be subclinical
 - Symptoms: dyspnea, dry cough
 - Fifty percent clear spontaneously
 - *Lymphadenopathy*: hilar, cervical, axillary, inguinal
 - *Ophthalmic*: anterior uveitis
 - *Cardiac*: ECG rhythm disorders owing to conduction abnormalities
 - *Gastrointestinal*: hematemesis, 10% with granulomas
 - *Neurologic*: facial palsy
 - *Renal*: overproduction of 1-25 dihydroxy vitamin D, increased Ca^{2+}
 - *Muscle*: biopsy: granulomas, no symptoms
 - *Bone*: If hands involved, check for bone cysts; joint pain in 25% to 40%
- Diagnosis
 - Histology
 - Naked (absent to sparse inflammation at periphery), noncaseating granulomas, Schaumann bodies (round, laminated, calcified)

- body), asteroid bodies (star-shaped eosinophilic structure)
- Must exclude infection, foreign-body reaction (zirconium, beryllium, silica, etc.), other inflammatory disorders (rosacea, cutaneous Crohn, etc.), and neoplastic disorders (granulomatous MF and sarcoidal response to underlying lymphoma)
- Chest x-ray:
 - Stage I: hilar adenopathy
 - Stage II: hilar adenopathy with infiltrates
 - Stage III: pulmonary infiltrates with adenopathy
 - Stage IV: end-stage fibrosis
- *Kveim-Siltzbach test*: injection of sarcoidal spleen extract into a patient with suspected sarcoid results in typical granulomatous reaction 4 to 6 weeks later; false-positive results are possible
- Laboratory studies
 - Angiotensin converting enzyme (ACE) levels may be elevated in two-thirds of patients; used for predicting disease progression with serial measurements
 - Increased erythrocyte sedimentation rate (ESR) in two-thirds of patients
 - Lymphopenia with a reduced CD4:CD8 ratio
 - 24-hour urine
 - Serum Ca^{2+} : elevated
- Treatment
 - Steroids suppress T-helper cells
 - Antimalarials [hydroxychloroquine (Plaquenil) and chloroquine (Aralen)]
 - Antimetabolites: methotrexate, chlorambucil, imuran
 - Minocycline
 - Retinoids
 - Thalidomide
 - Biologics that target T cells or TNF may be useful
- Although self-limited in duration, angioedema involvement of the upper respiratory tract may be life-threatening owing to laryngeal obstruction
- Recurrent episodes of urticaria and/or angioedema of <6 weeks' duration are considered acute; >6 weeks' duration are designated as chronic
- Pathology: dermal edema characterizes urticaria; edema of both the dermis and subcutaneous tissue characterizes angioedema; collagen bundles are widely separated, venules are often dilated, perivenular infiltrate may include lymphocytes, eosinophils, and neutrophils
- Classification based on etiology
 - *Ig-E dependent*: due to specific antigen sensitivity (pollens, foods, drugs, fungi, molds, *Hymenoptera* venom, helminthes)
 - Mechanism
 - ▲ A sensitized individual possesses IgE antibodies against a specific antigen
 - ▲ IgE antibodies are attached to the surfaces of mast cells
 - ▲ When rechallenged with the same antigen, the result is release of biologically active products from the mast cells, the most important being histamine
 - *Physical urticaria*: numerous types
 - *Dermographism*: linear wheals following minor pressure or scratching of the skin
 - *Solar urticaria*: characteristically occurs within minutes of sun exposure and often is a sign of erythropoietic protoporphyria
 - *Cold urticaria*: precipitated by exposure to the cold, and, therefore, exposed areas usually are affected
 - ▲ In some cases, the disease is associated with abnormal circulating proteins, more commonly cryoglobulins and less commonly cryofibrinogens and cold agglutinins
 - ▲ Additional systemic symptoms include wheezing and syncope, thus explaining the need for these patients to avoid swimming in cold water
- *Cholinergic urticaria*: precipitated by heat, exercise, or emotion; characterized by small wheals with relatively large flares; occasionally associated with wheezing
- **Complement-mediated**
 - Hereditary/acquired angioedema
 - ▲ Caused by C1 inhibitor (C1 IN—H) deficiency: hereditary angioedema (HAE)-low levels of the plasma protein C1 inhibitor (C1 INH)
 - ▲ Acquired angioedema (AAE) caused by consumption of C1 INH
 - ▲ C1 INH inhibits kallikrein and factor XIIa; therefore, kinin forming pathway is augmented when C1 INH is missing

Urticaria/Angioedema

- Edema formation in specific layers of the skin
- Clinical
 - *Urticaria* involves only the superficial portion of the dermis; presents as well-circumscribed wheals with erythematous, raised, serpiginous borders and blanched centers; may coalesce to become giant wheals; usually pruritic
 - Can involve any area of the body from the scalp to the soles of the feet
 - Appears in crops, with old lesions fading within 24 hours as new ones appear
 - *Angioedema* presents as well-demarcated, localized edema involving the deeper layers of the skin, including the subcutaneous tissue
 - Angioedema often occurs in the periorbital region involving the lips

- ▲ *Hereditary angioedema (HAE)*: type 1 (85%), autosomal dominant; suppressed C1 INH levels due to abnormal secretion or intracellular degradation; type 2 (15%), autosomal dominant, leads to synthesis of dysfunctional C1 INH, therefore, levels may be normal or elevated
- ▲ HAE: normal C1q, depressed C4 levels
- ▲ Occurs without accompanying urticaria
- ▲ Trauma often precipitates attacks
- ▲ Results in massive local swelling and occasionally fatal laryngeal edema
- ▲ *Acquired angioedema*: may be associated with B-cell lymphoma or connective tissue disease with consumption of C1 INH; may also be associated with autoimmune disorders with circulating IgG antibody to C1 INH
 - △ Acquired angioedema has depressed C1q levels and depressed C4 levels
- ▲ Bradykinin is the mediator of the swelling in both hereditary and acquired angioedema
- ▲ Angiotensin-converting enzyme inhibitors can cause angioedema: swelling also caused by increased bradykinin (due to a decreased degradation)
- *Serum sickness*
 - ▲ Due to deposition of immune complexes in blood vessel walls
 - ▲ Leads to fixation of complement and inflammation
 - ▲ Clinical: fever, urticaria, lymphadenopathy, myalgia, arthralgia, arthritis
 - ▲ Treatment: symptoms are self limited, last 4–5 days
- Reaction to blood product administration
 - ▲ Urticaria/angioedema may result from immune complex formation and complement activation that leads to direct vascular smooth muscle changes and indirectly via anaphylatoxins to mast cell mediator release
- Infections
 - ▲ Acute urticaria may be associated with upper respiratory tract infections due to viruses; hepatitis B virus has also been associated with urticaria
- Abnormalities of arachidonic acid Metabolism
 - ▲ Urticaria/angioedema may occur in response to aspirin
- **Nonimmunologic**
 - *Direct mast cell-releasing agents*: opiates, antibiotics, curare, D-tubocurarine, radiocontrast media
 - *Agents that alter arachidonic acid metabolism*: aspirin and other NSAIDs, azo dyes, benzoates
 - ▲ Blocks the production of prostaglandins from arachidonic acid

- ▲ The pathway is then shifted to the production of other metabolites, including leukotrienes
- ▲ Leukotriene release ultimately results in release of vasoactive substances (histamine) that alter vascular permeability and produce dermal edema (urticaria)

- **Idiopathic**

- *Chronic idiopathic urticaria*
 - ▲ Autoantibodies to the high-infinity IgE receptor or to IgE itself have been identified in these patients
 - ▲ Autoantibodies possess histamine-releasing activity
 - ▲ Wheals and itching daily for at least 6 weeks
 - △ Hashimoto thyroiditis and Grave disease are associated with CIU
 - △ Laboratory: thyroid function, antithyroid peroxidase, and thyroglobulin antibody titers

Urticarial Vasculitis (Immune Complex-Mediated)

- Sometimes a reflection of an underlying systemic illness such as lupus erythematosus, Sjögren syndrome, hereditary complement deficiency, serum sickness, or infections such as hepatitis B or C infection
- Individual erythematous wheals last longer than 24 hours and usually develop central petechiae that can be observed even after the urticarial phase has resolved
- On biopsy, there is a leukocytoclastic vasculitis of the small blood vessels
- Treatment
 - ▲ Any suspected medication should be discontinued
 - ▲ Avoidance of precipitating factors may be helpful for some of the physical urticarias, such as solar and cold urticaria
 - ▲ Symptomatic therapy usually includes H₁ antihistamines given on a regular rather than an intermittent, as-needed basis
 - ▲ The tricyclic antidepressant doxepin (Sinequan) is also effective and has been shown to have both H₁ and H₂ antihistamine activity

Graft-Versus-Host Disease (GVHD)

- Occurs when immunologically competent cells are introduced into an immunoincompetent host
- Most commonly seen in hematopoietic cell transplantation (HCT), both allogeneic (between two individuals) and autologous (from the same individual)
- Solid-organ transplants, blood transfusions, and maternal-fetal transfusions also have been reported to cause GVHD

- The skin often is the earliest organ affected
- GVHD remains a primary cause of morbidity and mortality after HCT
- Classifications: arbitrarily defined based on days from transplant
 - Acute GVHD
 - Occurs within the first 100 days of a transplant
 - Consists of a triad of dermatitis, enteritis, and hepatitis
 - Usually begins as scattered erythematous macules and papules that may evolve into a generalized erythroderma or bullous eruption
 - Mediated by T_H1 cells
 - Graded in five steps (0–IV)
 - ▲ Grade 0: no clinical evidence of disease
 - ▲ Grade I: rash on less than 50% of skin and no gut or liver involvement
 - ▲ Grade II: rash covering more than 50% of skin, bilirubin 2 to 3 mg/dL, diarrhea 10 to 15 mL/kg per day, or persistent nausea
 - ▲ Grade III or IV: generalized erythroderma with bullous formation, bilirubin greater than 3 mg/dL, or diarrhea more than 16 mL/kg per day
 - Chronic GVHD
 - Develops after 100 days
 - Consists of an autoimmune syndrome directed toward multiple organs
 - May occur as a late phase of acute GVHD or as a distinct entity
 - The skin is the primary organ involved and may be characterized as localized or generalized with lichen planus–like or sclerodermoid lesions commonly encountered
 - Mediated by T_H2 cells
- Pathophysiology
 - Three components are required for the development of GVHD
 - The graft must contain immunologically competent cells
 - The host must appear foreign to the graft
 - The host must be incapable of reacting sufficiently against the graft
 - Disease is caused by recognition of epithelial target tissues as foreign by the immunocompetent cells and subsequent induction of an inflammatory response and eventual apoptotic death of the target tissue (regardless of whether the immunoreactive T cells are derived from a nonidentical donor or from the recipient)
 - While T cells may orchestrate the initial inflammatory response, many cell types (e.g., $CD4^+$, $CD8^+$ T-cell subsets, natural killer cells) are found at sites of epithelial injury
- Histology
 - Acute: epidermal basal vacuolization, followed by epidermal basal cell apoptotic death with

lymphoid infiltration; satellite cell necrosis (direct apposition of a lymphocyte to a necrotic keratinocyte)

- Chronic: basal cell degeneration and necrosis, epidermal atrophy, and dermal fibrosis; lichenoid changes with mononuclear infiltrates, epithelial cell necrosis
- Treatment
 - Immunosuppression is the mainstay of therapy: limiting the graft-versus-host tissue response while maintaining the graft-versus-tumor effect is crucial
 - T-cell depletion with Campath 1H or thymoglobulin during transplant is useful
 - Prophylaxis with cyclosporine, mycophenolate mofetil, and tacrolimus is common; however, exacerbations of GVHD frequently require prednisone
 - Newer biologicals (CTLA-4-Ig, infliximab, etanercept, and anti-CD25 agents such as daclizumab) appear interesting and may prove useful
 - Immune modulation with photopheresis or phototherapy also has been helpful

Atopic Eczema (Atopic Dermatitis)

- Clinical: pruritic poorly demarcated, erythematous scaly patches, small vesicles, excoriations, crusting, lichenification and impetiginization that have a predilection for the skin flexures (neck, antecubital fossa, and popliteal fossa) in children and extensors in adults; chronic scratching and rubbing can lead to hyperpigmentation and lichenification; periorbital fold (Denny Morgan sign) may be present
- Pathogenesis
 - Believed to be multifactorial
 - Allergens (house dust mites, pollen, animal dander), outdoor pollution, climate, diet, and prenatal or early-life factors such as infections
 - Patients appear to have a genetic predisposition that can then be exacerbated by these numerous factors
 - Atopic skin has decreased human b-defensin 3 predisposing patients to frequent skin infections
- Histology: edema within the epidermis (spongiosis) and infiltration with lymphocytes and macrophages in the superficial dermis
- Diagnosis
 - Made by the typical morphology and distribution of the lesions
 - Family and personal history of atopy (asthma, allergic rhinitis, or atopic dermatitis) also can help with the diagnosis
- Prognosis
 - There is currently no cure; however, various interventions exist to control symptoms

- Can be expected to clear in 60% to 70% of children by their early teens, although relapses may occur
- Treatment
 - Includes emollients, oral antihistamines, topical corticosteroid ointments, topical tacrolimus, topical pimecrolimus
 - More severe cases sometimes use UV-B phototherapy or PUVA
 - Occasionally, a short course of systemic steroids is necessary to bring the disease under control
 - Steroid wet wraps and baths are helpful in treating acute atopic dermatitis
 - Avoidance of environmental factors that enhance itching is important
 - Moisturizers reduce dry skin and itching
 - Topical and/or oral antibiotics, bleach baths for bacterial superinfection

Nummular Eczema (Nummular Dermatitis)

- Occurs most frequently in patients who are in their fifties and sixties
- In temperate climates, this condition is seen most frequently in the winter
- More frequently encountered in patients of Asian descent
- The etiology is unclear, although xerosis plays a significant role in the pathogenesis
- Clinical
 - Pruritic, coin-shaped, erythematous patches that exhibit scale (hyperkeratosis) and occasionally pin-head sized vesicles on the legs, arms, and legs (in decreasing order of frequency)
 - Lesions may become excoriated and lichenified
- Treatment
 - Liberal use of emollients, avoidance of long hot showers, topical use of corticosteroids or immune modulators, and oral antihistamines
 - Severe cases may require UV-B phototherapy, PUVA, or oral corticosteroids

Seborrheic Dermatitis

- A common problem affecting 3% to 5% of the healthy population
- Waxing and waning course that parallels the increased sebaceous gland activity occurring in infancy and after puberty
- Clinical: erythematous patches and plaques with indistinct margins and yellowish, greasy-appearing scales affecting sebaceous hairy regions of the body (scalp, eyebrows, nasolabial creases, ears, chest, intertriginous areas, axilla, groin, buttocks and inframammary folds); variable amount of pruritus

- Refractory or more widespread disease may be associated with underlying HIV infection (approximately one-third of patients with AIDS and AIDS-related complex) or neurologic disorder (i.e., Parkinsons disease)
- Pathogenesis
 - Thought to be an inflammatory reaction to the resident skin yeast, *Pityrosporum ovale*
 - *P. ovale* is a lipophilic yeast that is normally found on the seborrheic regions of the skin
- Diagnosis: usually made on clinical grounds alone
- Treatment
 - Antiseborrheic shampoos containing zinc pyrithione, selenium sulfide, or ketoconazole are the mainstay of treatment
 - Topical steroids
 - Topical antifungals

Other Systemic Inflammatory Diseases

- Familial Mediterranean fever:
 - Autosomal recessive
 - MEFV gene; chromosome 16, mutation in the gene *pyrin* (*Marenostrin*)
 - Clinical findings: self-limited attacks of fever accompanied by peritonitis, pleurisy, and arthritis, erysipelas-like eruption on lower legs, urticaria, henoch-Schonlein purpura
 - Treatment: colchicines, anti-TNF
- Muckle-Wells
 - Autosomal dominant
 - CIAS1, encoding cryopyrin
 - Clinical findings: urticaria, fever, paresthesias, limb pain, deafness, renal, abdominal pain, polyarthralgia, conjunctivitis, systemic amyloidosis (25%)
 - Treatment: IL-1 receptor antagonist

QUIZ

Questions

1. A positive reaction resulting in skin induration to a tuberculin test is a:
 - A. Histamine-releasing immediate hypersensitivity reaction
 - B. Antibody and antigen (purified protein derivative) complex reaction
 - C. Antibody formation to the purified protein derivative
 - D. Plasma cell antibody response to purified protein derivative
 - E. T-cell response to purified protein derivative

2. A vesicular eruption on the lips following a sunburn is most likely caused by production of which cytokine?
 - A. IL-2
 - B. IL-4
 - C. IL-6
 - D. IL-10
 - E. IL-12
3. Low natural protection from developing skin ulcers following infection with *Leishmania braziliensis* are seen in patients with elevated production of what cytokine?
 - A. IL-12
 - B. IFN-gamma
 - C. IL-10
 - D. TNF-alpha
 - E. IL-13
4. Interferon-gamma_____.
 - A. Is a potent activator of macrophages
 - B. Promotes differentiation of lymphocytes
 - C. Leads to increased expression of MHC class I and II molecules
 - D. Activates leukocytes and endothelial cells
 - E. All of the above
5. Cytokines involved in decreased expression of human beta defensin-3 (HBD-3) and subsequent increased susceptibility to *Staphylococcus aureus* infections in atopic patients include all of the following EXCEPT:
 - A. IL-4
 - B. IL-10
 - C. IL-12
 - D. IL-13
 - E. None of the above
6. Pick the correct pairing of enzyme and end-product involved in arachidonic acid metabolism
 - A. Cyclooxygenase – thromboxanes, lipoxygenase – leukotrienes
 - B. Cyclooxygenase – prostaglandins, lipoxygenase – leukotrienes
 - C. Cyclooxygenase – leukotrienes, lipoxygenase – prostaglandins
 - D. Cyclooxygenase – leukotrienes, lipoxygenase – thromboxanes
 - E. None of the above
7. Which cytokine is an important activator of eosinophils?
 - A. IL-2
 - B. IL-3
 - C. IL-4
 - D. IL-5
 - E. IL-6
8. Which of the following statements regarding regulatory T cells is *false*?
 - A. Key cytokines are TGF-beta and TNF-alpha
 - B. They can be subsets of both CD4 + or CD8 + T cells
 - C. A mechanism of suppression is by secretion of IL-10
 - D. Cell-to-cell contact is a mechanism of suppressive activity
 - E. None of the above
9. The following statements regarding the innate immune system are all true EXCEPT:
 - A. The innate immune response is rapid
 - B. Pattern recognition receptors are highly conserved in phagocytic cells
 - C. Activation of toll-like receptors result release of cytokines in monocytes
 - D. Defensins are important in attracting immature dendritic cells
 - E. Recognition of antigen leads to clonal expansion of lymphocytes
10. Which of the following statements regarding complement activation is *false*?
 - A. Activation can occur via the lectin pathway independent of antibodies
 - B. Generation of C3b is common to all pathways
 - C. Antibody-antigen complexes activate the classical pathway
 - D. C3a and C5b are anaphylatoxins
 - E. The MAC complex forms transmembrane channels in the cell membrane

Answers

1. E. Skin induration in response to a tuberculin test is a delayed type hypersensitivity (type IV) reaction which involves T cells.
2. D. A sunburn results in local immunosuppression allowing activation of herpes simplex eruption. This process is mediated by IL-10, an immunosuppressive and anti-inflammatory cytokine.
3. C. Protection against *Leishmania* infection is conferred by Th1 dominant reactions. In Th2 polarized and mixed Th1/Th2 responses, infection and progression of disease can occur. Studies have shown that IL-10 is strongly elevated in Th2 and mixed responses.
4. E. Interferon-gamma exerts pleiotropic functions.
5. C. Research has shown that Th2 cytokines have been associated with down-regulated expression of HBD-3. Antagonizing IL-4, IL-10, or IL-13 allows for increased expression of HBD-3 on skin surfaces of atopic patients and improved *S. aureus* killing.

6. B. In inflammatory responses, arachidonic acid can be metabolized by many enzymes including cyclooxygenase (involved in production of prostaglandins, prostacyclin, and thromboxane) and lipoxygenase (generates leukotrienes).
7. D. IL-5 is a TH2 cytokine that can be produced by mast cells, T-helper cells, and eosinophils. IL-5 is a key activator of eosinophils.
8. A. Several naturally occurring and experimental populations of regulatory T cells have been recently identified. Suppressive effects have been shown to be mediated by cell to cell contact, production of IL-10 or TGF-beta. They can be either CD4+ or CD8+ T cells. Answer A is false because TNF-alpha, a pro-inflammatory cytokine, is incorrect.
9. E. All of the answers with the exception of answer E describes innate immunity. Recognition of antigen resulting in clonal expansion of lymphocytes is a feature of adaptive immunity.
10. D. C3a and C5a are anaphylatoxins that can trigger rapid reactions and induction of local inflammatory responses. Functions of C5a include triggering mast cell release of histamines, activation of neutrophils and macrophages, and as a chemoattractant for leukocytes. Complement C5b is not an anaphylatoxin but is part of the membrane attack complex.

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BASIC SCIENCES

KURT Q. LU
ASRA ALI

EPIDERMIS AND DERMIS

Epidermis

- Stratified squamous epithelium
- Approximately 0.4 to 1.5 mm thick and consisting mostly of keratinocytes (Fig. 28-1)
- Renewal of the epidermis takes approximately 26 to 28 days (13 to 14 days for maturation from basal layer to corneum and another 13 to 14 days for shedding)
- Divided into four main layers with characteristic cell shape, specialized intracellular structures, types of keratin, accessory cells, and proteins (Table 28-1): stratum corneum (SC), stratum granulosum, stratum spinosum, stratum germinativum
- *Stratum disjunction*: outer SC cells are more prone to desquamation
- *Stratum compactum*: cells of the lower stratum corneum; thicker cells and more densely packed, organized parallel arrays of keratin filaments, more fragile cornified envelope
- Stratum lucidum is an additional layer present between the strata granulosum and corneum in pal-moplantar skin. It appears as an electronlucent zone and contains nucleated cells
- Differentiation from basal cell to corneocyte involves the loss of the nucleus and extrusion of cellular contents except for keratin filaments and filaggrin matrix

SPECIALIZED CELLS

- Merkel cell
 - Type I mechanoreceptor (slow-adapting, low threshold)
 - Derived from ectoderm/neural crest
 - Mainly confined to basal layer
 - Present in areas with high tactile sensitivity (hairy and glabrous skin)
 - Typically found in epithelium of digits, lips, oral cavity, and outer root sheath of the hair follicle

- Contain granules with neurotransmitter-like substances; nonspecific enolase present
- Members of the amine precursor uptake and decarboxylation (APUD) system
- Keratins found in merkel cells: K20 is specific; also contain K18, K8, K19
- Melanocytes
 - Neural crest-derived dendritic cell
 - Mainly confined to basal layer
 - Extend above and below basal layer but do not form junctions with keratinocytes
 - Contains two types of the pigment melanin
 - Eumelanin (brown and black coloration)
 - Pheomelanin (red or yellow coloration)
- Langerhans cell
 - Dendritic, bone marrow-derived (mesoderm) antigen-presenting cell
 - Involved in T-cell responses (i.e., contact hypersensitivity and graft-versus-host disease)
 - Process antigen and present it to T cells in the presence of major histocompatibility complex (MHC) class II
 - Produces interleukin 1 (IL-1)
 - Contains distinctive racket-shaped Birbeck granules that are formed when an antigen is internalized by endocytosis
 - Ultraviolet B (UV-B) decreases number and antigen-presenting ability of Langerhans cell
 - Can be infected with HIV
 - Reduced numbers in patients with psoriasis, sarcoidosis, and contact dermatitis

SPECIALIZED STRUCTURES

- Desmosomes
 - Prominent in the stratum spinosum
 - Anchoring junctions that connect adjacent keratinocytes (Fig. 28-2)
 - Keratin filaments extend from desmosome to desmosome to form keratin cytoskeleton

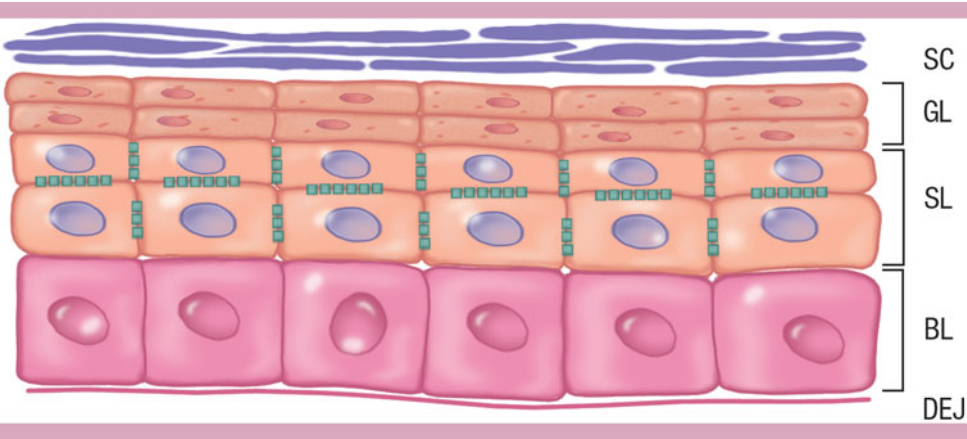


FIGURE 28-1 Epidermis. (Reprinted with permission from Wolff, K et al. *Fitzpatrick’s Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

TABLE 28-1 Layers of the Skin and Characteristics

	Cell Shape	Types of Cells	Types of Keratin	Additional Structures	Associated Proteins
Stratum corneum Stratum disjunctum (outer stratum corneum cells)	Flattened polyhedral-shaped horny cells with loss of nucleus	Keratinocytes		Cornified cell envelope	Loricrin Profilaggrin Filaggrin Involucrin
Stratum compactum (cells of the lower stratum corneum)					Cornifin Trichohyalin TGM 1/2/3 Envolplakin SPR 1/2
Stratum granulosum	Diamond-shaped with characteristic dense basophilic granules		K2 K11	Basophilic keratohyaline granules	Profilaggrin Loricrin
Stratum spinosum	Polyhedral with round nucleus; “spiny appearance”	Keratinocytes Langerhans cell Transient amplifying cells	K1 K10 K9	Lamellar granules Desmosomes Gap junctions	Desmoglein II/III Desmocollin I
Stratum germinativum	Columnar with round nucleus	Keratinocytes stem cells (10%) Transient amplifying cells (50%) Postmitotic differentiated cells (40%) Melanocytes Merkel cell Langerhans cell	K5 K14 K19		BPAG 1

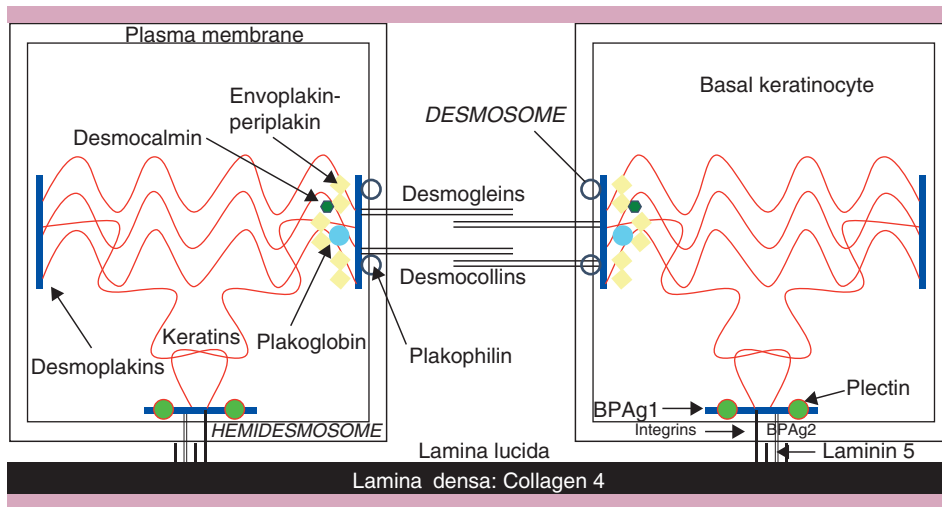


FIGURE 28-2 Desmosomes. (Modified with permission from Freedberg IM et al. *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill, 2003; p. 93.)

- Structure consists of a desmosomal plaque on the interior of the cell membrane, transmembrane glycoproteins, and a central plate that crosses the intercellular space between two keratinocytes
- Plaque contains six polypeptides
 - Desmoplakins 1 and 2—mediate attachment of keratins to plaque
 - Desmocalmin—important for calcium regulation
 - Band 6 protein
 - Plakoglobin—mediates attachment of keratins to plaque
 - Desmoyokin—associated with cell membrane
- Transmembrane proteins are cadherins (Ca^{2+} dependent cell-cell adhesion molecules) and provide adhesion
 - Desmogleins 1 and 3
 - Desmocollins I and II
- Tight junctions
 - Regulates epidermal barrier permeability
 - Composed of structural proteins called claudins
 - Mutation in claudin-1 has been linked to a rare ichthyosis
- Gap junctions
 - Allow for communication between cells
 - Made of connexins
 - Mutation in connexin-26 results in Vohwinkel's syndrome and keratitis-ichthyosis-deafness syndrome (KID)
 - Mutation in connexin-30 results in Clouston's syndrome
 - Mutation in connexin-30.3 and 31 result in erythrokeratoderma variabilis
- Adherens junctions
 - Associates with actin cytoskeleton
 - Made of "classic cadherins" (E-, P-, and N-cadherins) which are calcium-dependent
 - Sites of contact between neighboring keratinocytes or Langerhans cells
- Actin attaches to cadherins via alpha, beta, and gamma catenins
- Lamellar granules (Odland bodies)
 - First apparent in upper spinous layer, but primary site of action is the granular layer
 - 0.2 to 0.3 μm in diameter, membrane-bound secretory granules
 - Contain glycoproteins, glycolipids, phospholipids, free sterols, acid hydrolases, and glucosylceramides (precursors to ceramides that contribute to corneum lipid layer)
 - Extrude their contents of lipids and enzymes into the intercellular space, where the lipid is rearranged to lipid sheets
 - Create a hydrophobic barrier between the granular and cornified layers
- Keratohyaline granules
 - Dense basophilic granules containing electrondense proteins of profilaggrin, keratin, and loricrin
 - Filaggrin (cleaved from profilaggrin) becomes the major protein of keratohyaline granules
 - Involved in formation of cornified cell envelope
 - Rich in sulfur
- Cornified cell envelope (CCE)
 - An extremely durable protein-lipid polymer
 - Assembled on the interior of the keratinocyte
 - Eventually resides on the exterior of the corneocyte
 - Provides a mechanical and chemical barrier
 - CCE is 7 to 15 nm thick
 - Impermeability of this layer is achieved by the action of calcium-dependent transglutaminases that bind (cross-link) loricrin, keratin, desmosomal proteins, involucrin, elafin, and other proteins to the cell membrane, creating a proteinaceous and insoluble shield
 - Epsilon-gamma-glutamyl-lysine-isopeptide crosslinks make the CCE insoluble

SPECIALIZED PROTEINS

- Profilaggrin/filaggrin (*filament aggregate protein*)
 - Profilaggrin is a protein made up of 10 to 12 tandem repeat units of filaggrin
 - Profilaggrin is converted to monomers of filaggrin in a stepwise conversion by three proteases and dephosphorylation
 - Filaggrin is thought to provide a protein matrix for keratin filament aggregation in corneocytes
- Loricrin
 - A protein composing 70% of the CCE
 - Hydrophobic, cysteine-rich protein
 - Gene is located on chromosome 1q21 as part of the epidermal differentiation complex
 - Encoded along with other proteins required for the terminal differentiation of epidermis
 - Loricrin is localized to the desmosome in association with desmoglein
- Involucrin
 - Glutamine-rich, acidic protein
 - Resistant to denaturing and unchanged by retinoic acids
 - Early marker of keratin differentiation
 - Serves as a scaffold for other proteins to bind during keratinization
- Meissner corpuscles
 - ▲ Located in dermal papillae
 - ▲ Detect light pressure
 - ▲ More prevalent in palms and soles
 - ▲ “Pine cone” appearance
- Vater-Pacini corpuscles
 - ▲ Located in deep dermis of palms, dorsum of hands, and soles; also skin of nipples and anogenital region
 - ▲ Detect deep pressure and vibration
 - ▲ “Pearl onion” appearance in cross section
- Mucocutaneous end organs (Krause end bulbs)
 - ▲ Located in papillary dermis
 - ▲ Found in skin at mucocutaneous junction (vermillion border of lips, glans penis, clitoris)

DERMAL-EPIDERMAL JUNCTION**Dermis**

- Mesodermal origin
- Collagen is major protein composed of fibroblasts. Mainly type I in adult skin, type III fetal skin
- Two regions
 - Papillary dermis
 - Superficial
 - Small collagen bundles
 - Fine meshwork of microfibrils (fibrillin) organized into elastin and oxytalan fibers
 - Reticular dermis
 - Below papillary dermis
 - Large collagen bundles
 - Mature, branching elastic fibers
- Main components of dermis:
 - Ground substance (mucopolysaccharides)
 - Subpapillary vascular plexus
 - Deeper vascular plexus that envelops hair follicles and eccrine sweat glands
 - Fibroblasts, macrophages, and mast cells
 - Afferent nerves (stain for S-100)
 - Unmyelinated nerve fibers (C-type fibers)
 - ▲ Detect temperature, pain, and itch
 - ▲ Located in papillary dermis and possibly basal layer
 - ▲ Encapsulated nerve endings detect touch and pressure
- Also referred to as the *basement membrane zone* (BMZ)
- Thickness of 0.5 to 1.0 mm
- Visualized with periodic acid–Schiff (PAS) staining, not hematoxylin and eosin (H&E) stain
- Most components arise from basal keratinocytes or fibroblasts
- Function
 - Supportive structure to anchor the epidermis to the dermis: anchoring occurs through the cytoskeleton in keratinocytes that bind to laminin 5 in the lamina lucida, which, in turn, binds to type VII collagen in lamina densa
 - Regulates interactions between the dermis and epidermis
 - Provides a selective barrier between the dermis and epidermis
- Hemidesmosome (anchoring complex) (Fig. 28-3)
 - Attaches basal cells of epidermis to the basement membrane (link keratin cytoskeleton to laminin 5 in the lamina lucida)
 - Structurally different from desmosomes
 - Consists of a cytoplasmic portion (attachment plaque), transmembrane portion [bullous pemphigoid (BP) antigen 2 (180 KD) and integrin, and an extracellular portion (anchoring filaments and subbasal dense plate)]
 - Cytoplasmic attachment plaque
 - Consists of BP antigen 1 (230 KD) and plectin (HD-1)
 - Keratin filaments (K5, 14) attach to plaque
 - Desmocalmin and desmoplakin bind keratin to plaque
 - Intracellular portion of BP antigen 2 (180 KD) (BPAG2) and collagen XVII are also present
 - Transmembrane portion
 - Consists of BP antigen 180 (BPAG2)—type II transmembrane configuration

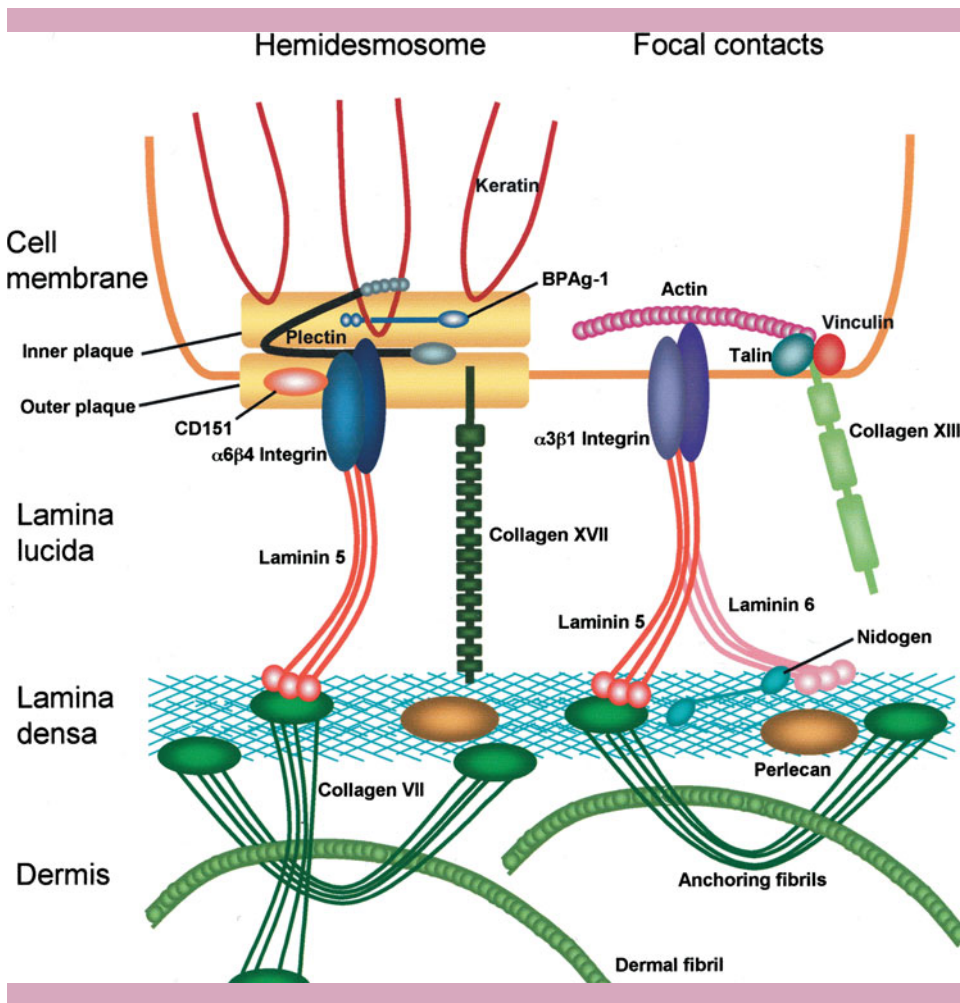


FIGURE 28-3 Hemidesmosome. (Reprinted with permission from Freedberg IM et al. *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003, p. 195.)

- Contains $\alpha 6 \beta 4$ integrin, which likely interacts with laminin 5 to form anchoring filaments
- Subbasal dense plate and anchoring filaments
 - Located below the hemidesmosome in the lamina lucida
 - Integrins and BPAg2 cross the membrane and attach to plate
 - Anchoring filaments then extend from the subbasal plate into the lamina densa, providing a point of deeper attachment
- Three zones of basement membrane zone
 - *Lamina lucida*
 - Named for appearance on electron microscopy (EM) as electron-lucent
 - 8 nm wide
 - Weakest of layers—able to split with heat or salt
 - Composed of laminin 1, nidogen (entactin), and fibronectin
 - Anchoring filaments cross lamina lucida
 - ▲ Filaments contain laminin-322 (composed of one $\alpha 3$, $\beta 3$, and $\gamma 2$ chain), formerly known as laminin 5 (aka. epiligrin, kalinin, and nicein)
 - *Lamina densa*
 - Composed of type IV collagen (unique to dermal-epidermal junction)
 - Also contains entactin (nidogen): binds laminin, collagen IV, perlecan, and fibulins (calcium-binding extracellular matrix proteins)
 - Also contains fibulins (calcium-binding extracellular matrix proteins)
 - ▲ Fibulins function to support the structural network of different basement membranes by joining other supramolecular structures, elastic fibers, and aggregates
 - ▲ Can be found in basement membranes and vessel walls
 - ▲ Fibulin-1 mutation results in Marfan Syndrome
 - ▲ Fibulin-2 binds fibrinogen, fibronectin, nidogen, proteoglycans, aggrecan, and versican

- Contains heparan sulfate proteoglycan, which is negatively charged owing to disulfide bridges and renders the dermal-epidermal junction impermeable to negatively charged substances
- *Sublamina densa*
 - Contains network of anchoring fibrils composed of type VII collagen
 - Anchoring fibrils originate in lamina densa, dip down into the dermis, and attach to an anchoring plaque or loop back to reinsert into the lamina densa
 - Fibrils appear as “wheatstacks” on EM
 - Contains interstitial collagen fibers of types I, III, V, and VI
 - Contains microfibrils composed of fibrillin: two types of microfibrils
 - ▲ Elaunins—horizontal
 - ▲ Oxytalins—perpendicular to elaunins
 - Contains microthread-like fibers of the glycoprotein linkin

TABLE 28-2 Classification of Keratins

Type I	Type II
Acidic (pK 4.5–5.5)	Basic or neutral (pK 5.5–7.5)
Smaller in size (40–56.5 kDa)	Larger in size (52–67 kDa)
Keratins K9–K20 Hal to Ha4, Hax	Keratins K1–K8 Hb1 to Hb4, Hbx
Chromosome 17q12-21	Chromosome 12q11-13

KERATINS

Classification of Keratins

- Members of the structural protein group of intermediate filaments (named for their assembled diameter of 10 nm)
- Six types of intermediate filaments (types I to VI)
- Keratins make up type I and type II intermediate filaments
- Approximately 40 varieties of keratin
- Spontaneously form pairs consisting of a type I and a type II; an acidic and a basic protein, respectively. (Table 28-2)

Structure of Keratins

- Polypeptides consisting of a central rod domain of approximately 310 amino acids (Fig. 28-4)
- Central domain is composed of four highly conserved alpha-helical regions (designated 1A, 2A, 1B, and 2B)
- Regions are connected by three nonhelical linking sequences thought to provide flexibility (designated L1, L12, and L2)
- Central domain is flanked by an amino head and carboxy tail
- Two keratin polypeptides (one type I and one type II) combine to form a parallel coiled coil
- Coil is stabilized by hydrophobic interactions between the two strands; structure is now a keratin heterodimer
- Keratin heterodimers form long chains in a head-to-tail sequence
- Two chains of keratin heterodimers then combine in antiparallel fashion to form a protofilament (2 to 3 nm)
- Two protofilaments combine to form a protofibril (4.5 nm)
- Protofibrils then assemble in groups of three or four strands to form a 10-nm intermediate filament of keratin

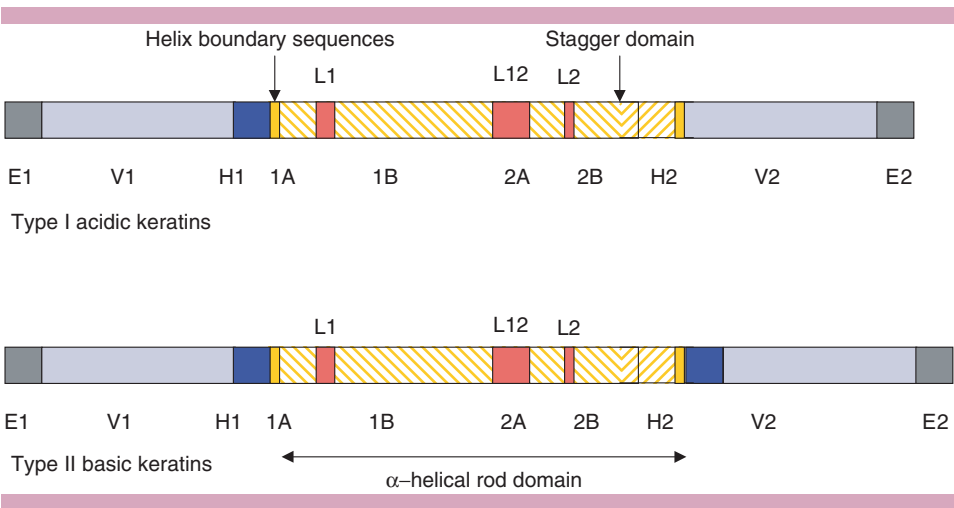


FIGURE 28-4 Keratin polypeptides. (Reprinted with permission from Freedberg IM et al. *Fitzpatrick’s Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill, 2003, p. 96.)

Keratins in Disease

- Mutations affecting the ends of the central domain prove the most deleterious (Table 28-3)

ADHESION MOLECULES

- Adhesion molecules contribute to
 - Cell-to-cell adhesion
 - Interaction between cells
 - Cell signaling
 - Inflammation
 - Migration of cells
 - Wound healing
 - Embryogenesis
- Families of adhesion molecules
 - **Cadherins**
 - Calcium-dependent cell-cell adhesion molecules
 - Main adhesion molecule in early embryogenesis
 - Structure: single-pass transmembrane glycoprotein
 - Bind to catenins (link cytoskeleton to adherens junction)
 - Two types
 - ▲ Classic cadherins—found at adherens junctions and interact with cytoplasmic anchoring structures
 - △ E cadherin: found on all epithelium; Chromosome 16q
 - △ N cadherin: found on nerve, muscle, epithelium
 - △ P cadherin: found on placenta and basal epithelium
 - ▲ Desmosomal cadherins—found in desmosomes; associate with keratin filaments via plakoglobin and desmoplakin
 - △ Desmoglein—membrane-bound; pemphigus vulgaris—autoimmunity against desmoglein 3; pemphigus foliaceus—autoimmunity against desmoglein 1
 - △ Desmocollins—membrane bound

TABLE 28-3 Keratin Expression Patterns and Keratin-Associated Diseases

Type II	Type I	Physiologic Location of Expression	Hereditary Diseases
1	10	Suprabasal keratinocytes	Bullous congenital ichthyosiform erythroderma
1	9	Palmoplantar suprabasilar keratinocytes	Epidermolytic PPK Diffuse nonepidermolytic PPK Epidermolytic PPK with polycyclic psoriasiform plaques
2e	10	Upper spinous and granular layer	Ichthyosis bullosa of Siemens
3	12	Cornea	Meesmann's corneal dystrophy
4	13	Mucosal epithelium	White sponge nevus
5	14	Basal keratinocytes	Epidermolysis bullosa simplex
6a	16	Outer root sheath, hyperproliferative keratinocytes, palmoplantar keratinocytes	Pachyonychia congenita type I, focal nonepidermolytic PPK
6b	17	Nail bed, epidermal appendages	Pachyonychia congenita type II Steatocystoma multiplex
8	18	Simple epithelium	Cryptogenic cirrhosis
	19	Embryonic	
Hb, 1, 3, 5, 6	Ha 1, 2, 3a, 3b, 4–8	Hair follicle	Monilethrix (Hb1 and 6)

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- △ Plakoglobin—cytoplasmic
 - △ Desmoplakin—cytoplasmic: only molecule known to be present in both desmosomes and adherens junctions
- **Integrins**—integrate intracellular cytoskeleton with extracellular matrix
 - Large family of transmembrane molecules composed of two noncovalently bound polypeptide subunits (α , β)
 - Most integrins recognize and bind peptide sequence of arginine-glycine-aspartic acid (commonly found on matrix proteins like collagen)
 - Subfamily depends on β subunit:
 - $\beta 1$ —binds cells to extracellular matrix: This subfamily is also known as VLA (very late activation) 1–6
 - $\beta 2$ —binds leukocytes to endothelium or other inflammatory cells
 - ▲ Three members: leukocyte function antigen-1 (LFA-1), macrophage activation antigen 1 (Mac 1), and p150, 95
 - ▲ Abnormality leads to leukocyte adhesion problems and chronic infection/abscess
 - $\beta 3$ —interaction between platelets and neutrophils at sites of inflammation or vascular damage: contains two members: platelet glycoprotein IIb/IIIa and vitronectin receptor
 - $\beta 4$ — $\alpha 6\beta 4$ is the most notable of this subfamily
 - ▲ Localized to hemidesmosomes of basement membrane
 - ▲ Binds to laminin 5 in anchoring filaments
 - ▲ Plays an important role in junctional epidermolysis bullosa
 - Summary of integrins (Table 28-4)
- **Selectins**
 - Family of proteins that function in cell-cell adhesion; mediate recruitment of inflammatory cells
 - Three classes
 - ▲ L-selectin (leukocyte): expressed on leukocytes
 - ▲ P-selectin (platelet)
 - △ Stored preformed in Weibel-Palade bodies of endothelium; released rapidly to membrane in response to stimulation and then can be reinternalized
 - △ Also found on alpha-granules of platelets and megakaryocytes
 - ▲ E-selectin (endothelial): produced on endothelial cells in response to IL-1 and tumor necrosis factor (TNF)
- **Immunoglobulin supergene family**
 - Extensive group of cell surface-binding proteins that contain one or more Ig/Ig-like domain (disulfide-bridged loops)
 - *Cellular adhesion molecule* (CAM)
 - Primary function is antigen recognition and cell-cell adhesion
 - Can be inducible or constitutively expressed on endothelium
 - Members
 - ▲ Intercellular adhesion molecule 1 (ICAM 1) CD 54
 - △ Expressed constitutively on endothelial cells, certain epithelial cells, and antigen presenting cells
 - △ Can be induced for surface expression on other cells by cytokines (α IFN)
 - △ ICAM 1 allows inflammatory cells to attach and infiltrate lesions in skin (e.g., psoriasis)
 - △ Ligand is LFA-1
 - △ Interaction of LFA-1 and ICAM allows T cells to come into close contact with an antigen-presenting cell (APC), which is a key step in activating a T-lymphocyte
 - △ ICAM 1 is the receptor for rhinovirus on respiratory epithelium
 - ▲ Intercellular adhesion molecule 2 (ICAM 2)
 - △ Constitutively expressed
 - △ A second ligand for LFA-1
 - ▲ Leukocyte function antigen 3 (LFA-3) CD 58
 - △ Expressed on APCs and forms a ligand with CD2 receptor on T-cell surface
 - △ This is a secondary signal in the activation of T cells
 - △ Important target for current psoriasis therapies
 - ▲ Vascular cell adhesion molecule 1 (VCAM 1)
 - △ Expressed on endothelial cells on activation
 - △ Expression induced by IL-1 and TNF- α
 - △ Directly involved in endothelium-lymphocyte interactions
 - △ Mediates recruitment of lymphocytes into areas of inflammation

COLLAGEN

- Produced by ribosomes within fibroblasts
- Provides structural stability
- Represents 70% to 80% of dry weight of the dermis
- Basic collagen structure is three alpha chains combined in a triple-helix formation with cross-linking hydrogen bonds

TABLE 28-4 Summary of Integrins

Integrin	Alternate Name	Expressed on	Matrix Ligand	Endothelial Ligand
β1 Subfamily				
α1β1	VLA-1	T cells	Collagen I, IV Laminin	
α2β1	VLA-2	T cells	Collagen I, IV Laminin	
α3β1	VLA-3	T cells	Collagen Laminin 1, 5 Fibronectin Epiligrin	
α4β1	VLA-4	T cells	Fibronectin	VCAM-1
α5β1	VLA-5	T cells	Fibronectin	
α6β1	VLA-6	T cells	Laminin	
β2 Subfamily				
α1β2	LFA-1	Neutrophils Monocytes		ICAM-1 ICAM-2
αmβ2	Mac-1	Neutrophils Monocytes	C3bi Fibronectin	ICAM-1
αxβ2	P150, 95	Neutrophils Monocytes	C3b Fibronectin	
β3 Subfamily				
Platelet Glycoprotein Iib/IIIa		Platelets	Fibrinogen Fibronectin von Willebrand factor Vitronectin	
Vitronectin Receptor			Vitronectin Fibrinogen vWF	
β4 Subfamily				
α6β4		Keratinocytes (basal)	Laminin 1, 5	

- Nineteen types of collagen
- Typical sequence of collagen: GLY—X—Y (Fig. 28-5)
 - GLY = glycine, always the third residue, 33 % of amino acids in collagen
 - X = frequently proline
 - Y = frequently hydroxyproline or hydroxylysine
- Four classes of collagen
 - Fibrillar collagen—types I, II, III, and XI
 - Network-forming collagens (nonfibrillar)—type IV
 - Microfibrillar—VI, VII
- FACIT (fibril-associated collagens with interrupted triple helices)—IV, XII, XIV
- Collagen biosynthesis (Fig. 28-6)
 - Pretranslational
 - Occurs in the nucleus
 - Transcription of genes for procollagen
 - mRNA is formed
 - Cotranslational
 - mRNA is transferred to ribosomes of rich endoplasmic reticulum (RER)

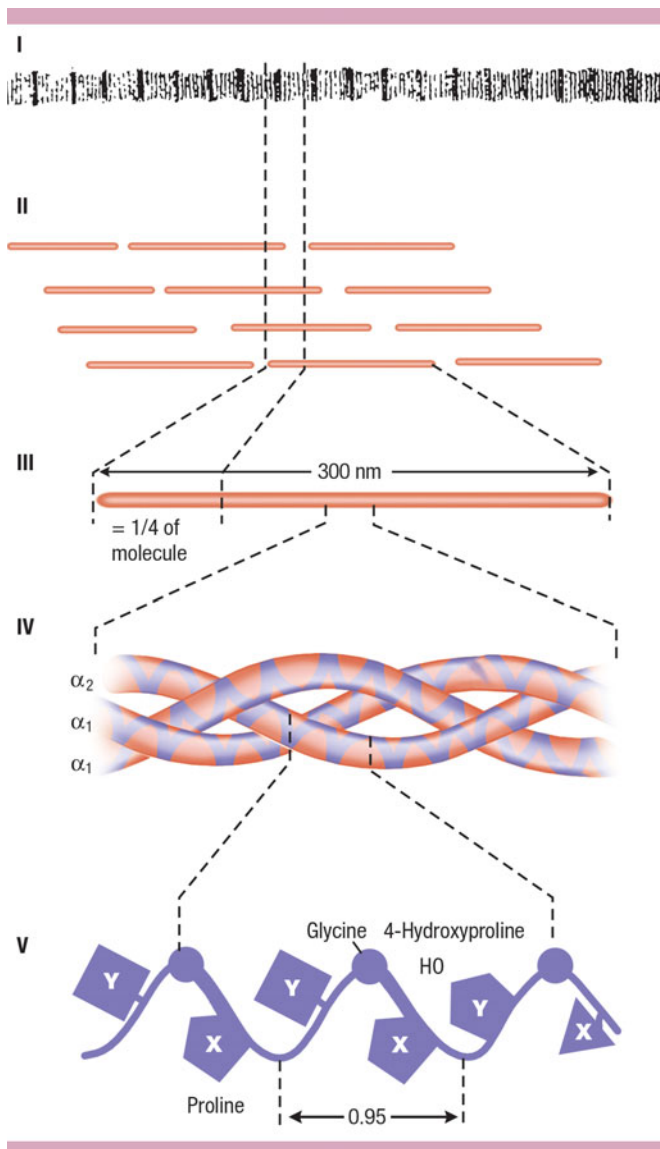


FIGURE 28-5 Typical sequence of collagen. (Reprinted with permission from Wolff K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- Pre-procollagen is formed and contains a signal peptide that indicates that the peptide is to be excreted from the cell
- During passage through the RER the following occurs
 - ▲ Hydrolytic cleavage of signal peptide
 - ▲ Hydroxylation of proline and lysine residues by prolyl hydroxylase or lysyl hydroxylase (deficient in type VI Ehlers-Danlos syndrome); hydroxylation requires oxygen, vitamin C, ferrous iron, α -ketoglutarate
 - ▲ Glycosylation of hydroxylysine residues and asparagine with N-linked oligosaccharides

- Postranslational
 - While in the RER, three procollagens are aligned and form disulfide bonds between chains to stabilize the structure; this occurs first on the amino end and then on the carboxy end
 - Three procollagens form a triple helix (carboxy-to-amino end)
 - Procollagen is transferred from the RER to the Golgi complex and is secreted continuously from the cell into the extracellular space
 - Once excreted, neutral calcium-dependent proteinases cleave the extra peptide extensions on the end of the procollagen to form tropocollagen
 - Tropocollagen then combines to form collagen fibrils, which are stabilized by cross-links
 - Cross-linking is catalyzed by lysyl oxidase, which uses copper as a required cofactor (enzyme is defective in type IX Ehlers-Danlos syndrome)
 - Fibrils combine to create a collagen fiber
- Factors that affect collagen production
 - Ascorbic acid—stimulates
 - Transforming growth factor β (TGF- β)—stimulates
 - IL-1—inhibits by stimulating PGE2
 - Glucocorticoids—inhibit collagen gene transcription
 - Retinoic acid—increases collagen synthesis
 - Interferon- γ (INF- γ)—potent inhibitor of collagen gene transcription
 - TNF- α —inhibits gene transcription
 - D-Penicillamine—interferes with collagen cross-linking
 - Minoxidil—inhibits expression of lysyl hydroxylase
 - Distribution of types of collagens (Table 28-5)
 - Heritable connective tissue diseases (Table 28-6)

ELASTIC TISSUE

- Allows skin to return to normal shape after being deformed or stretched
- Composed of elastic fibers
- Elastic fibers are visualized with special stains: Verhoeff-van Gieson, Orcein, or Resorcin-Fuchsin
- Elastic fibers are made of protein filaments embedded in an amorphous matrix of mostly elastin; this elastin core is surrounded by microfibrils that contain fibrillin
- Papillary dermis—elastic fibers are thin and run perpendicular to the skin surface; named *oxytalan fibers*
- Reticular dermis—elastic fibers are thick and run parallel to the skin surface; named *elaunin fibers*
- Elastin

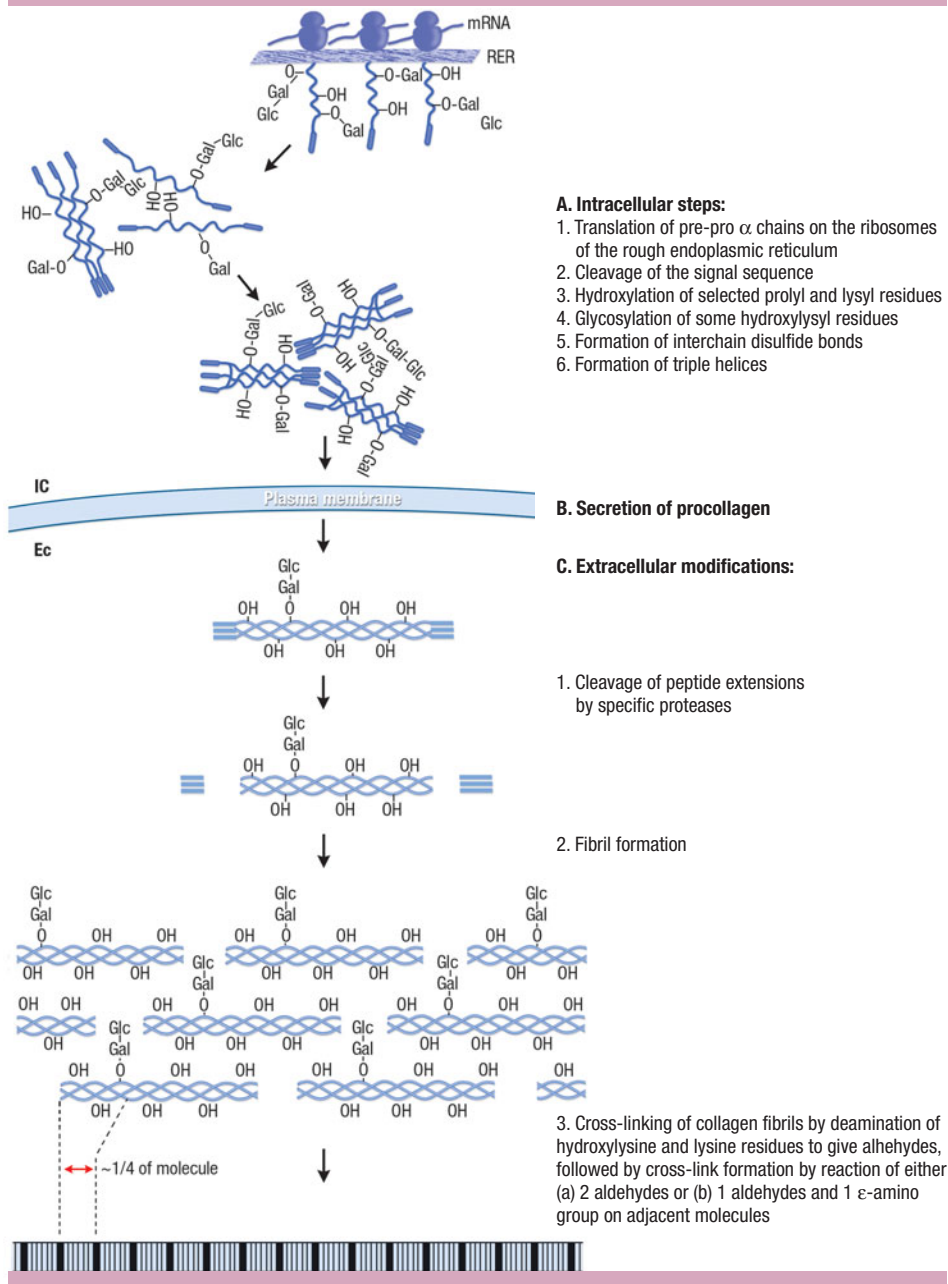


FIGURE 28-6 Collagen biosynthesis. (Reprinted with permission from Wolff K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- Secreted mainly by skin fibroblasts
- Elastin is mapped to chromosome 7
- Composed primarily of glycine, alanine, valine, proline, and lysine
- Elastin contains the unique amino acids of desmosine and isodesmosine
 - These amino acids provide sites for cross-linking (catalyzed by lysyl oxidase); cross-linking creates stability and insolubility
 - Desmosine is formed in the extracellular space by oxidative deamination of lysyl residues to allysine and then the fusion of three allysines with a lysyl residue
- This is catalyzed by the enzyme lysyl oxidase, with copper and oxygen as cofactors
- Anetoderma = loss and fragmentation of skin owing to decreased desmosine
- Expression of elastin is activated early in embryogenesis and continues at a steady rate until age 40, when it drops off precipitously
- Degradation of elastic fibers occurs by elastases (proteolytic enzymes)
 - Classic elastases—degrade insoluble elastic fibers at neutral or mildly alkaline pH; found in polymorphonuclear cells (PMNs); inhibited by α_1 -antitrypsin, α_2 -macroglobulin

TABLE 28-5 Distribution of Types of Collagens

Collagen	Distribution
I	Skin, bone, tendon, dentin (80% of total adult collagen)
II	Cartilage, vitreous
III	Blood vessels, gut, fetal skin (predominant cartilage), chorioamnion
IV	Basement membrane (lamina densa), epidermal appendages, blood vessels
V	Wide spread except in hyaline cartilage
VI	Aortic intima, placenta
VII	Anchoring fibrils, amnion
VIII	Endothelial cells, cornea
IX	Cartilage
X	Cartilage (hypertrophic)
XI	Cartilage
XII	Cartilage, fibroblasts, FACIT collagen, perichondrium, periosteum, cornea
XIV	Cartilage, skin, tendons, muscle, placenta, FACIT collagen
XV	Placenta, basement membrane
XVI	Placenta
XVII	Hemidesmosomes (bullous pemphigoid antigen 2)
XVIII	Placenta, liver, kidney, basement membrane
XIX	Rhabdomyosarcoma, basement membrane

- Elastase-like metalloproteases—degrade soluble elastin, oxytalan, and elaunin fibers; cannot degrade insoluble elastases; requires calcium
- Diseases with elastic fiber abnormalities (Table 28-7)

GROUND SUBSTANCE

- Component of connective tissue of dermis
- Consistency of a viscous solution or thin gel
- Stains with PAS or with toluidine blue

- Consists of several types of proteoglycans
- Proteoglycans (PGs)
 - Macromolecule with a core of protein and covalently attached glycosaminoglycans (GAGs)
 - Abundance of hydroxyl, carboxyl, and sulfate groups make proteoglycans hydrophilic and polyanionic; this creates an intensely hydrated molecule that can bind up to 1000 times of its own volume
 - This hydration affects volume and compressibility of the dermis
 - PGs also play a role in binding growth factors and acting as adhesion sites for other molecules
- Glycosaminoglycans—repeating units of disaccharides (Table 28-8)
- Skin conditions associated with GAG is:
 - Mucopolysaccharidoses (Hunter's, Hurler's, San Filippo) result from defective lysosomal enzymes; the defect causes accumulation of GAGs in many tissues
 - Aging results in increases of dermatan sulfate and decreases in chondroitin-6-sulfate
 - In wound healing, hyaluronic acid increases shortly after injury and then decreases as chondroitin sulfate increases

MELANOCYTES

- Melanocytes are derived from neural crest cells
- Melanocyte function, development, and differentiation are under the control of the paired box (PAX3) and the microphthalmia-associated transcription factor (MITF) genes. (Mutations in PAX3 and MITF results in Waardenburg syndrome.)
- Melanocytes migrate dorsoventrally in the eighth week of fetal development
- Melanin synthesis begins in the head region in the third month of fetal development
- Melanin is also found in the retina, uvea, cochlea/ vestibular apparatus, and leptomeninges; therefore, diseases of skin pigmentation also may have abnormalities in these areas
- In all races, density of melanocytes is a consistent ratio of about one melanocyte for every ten keratinocytes
- Melanocytes reside in the basal layer and send dendrites containing melanosomes (containing the pigment melanin) into contact with keratinocytes
- Melanocytes do not form desmosomes with adjacent keratinocytes; they may form contact via E-cadherin adhesion molecules
- Melanocytes do not form hemidesmosomes with the basement membrane
- Melanosomes
 - Melanosomes are secretory organelles developed from specialized exocrine cells of neural crest origin

TABLE 28-6 Heritable Connective Tissue Diseases With Cutaneous Involvement

Disease	Inheritance*	Mutated Genes†	Affected Protein
Ehlers-Danlos syndrome	AD, AR	COL1A1, COL1A2, COL3A1, COL5A1, COL5A2	α Chains of types I, III, and V collagens
	~	PLOD	Procollagen-lysine 2-oxoglutarate 5-dioxygenase (lysylhydroxylase)
		ADAMTS-2	Procollagen N-peptidase
		TNX	Tenascin-X
		B4GALT-7	Xylosylprotein 4-beta-galactosyltransferase
Osteogenesis imperfecta	AD, AR,	COL1A1, COL1A2	$\alpha 1$ and $\alpha 2$ Chains of type I collagen
Cutis laxa	AD, AR, XR†	ELN MNK-1 (ATP7A)	Elastin ATP-dependent copper transporter
Homocystinuria	AR	CBS	Cystathionine β -synthase
Menkes' syndrome	XR	MNK-1 (ATP7A)	ATP-dependent copper transporter
Focal dermal hypoplasia	XD	ND	
Tuberous sclerosis (shagreen patches)	AD	TSK-1 TSC 1 plus 2	Hamartin 1 Tuberlin
Familial cutaneous collagenoma	AD	ND	
Epidermolysis bullosa VII and XVII collagens	AD, AR	COL7A1, COL17A1	$\alpha 1$ Chains of types VII and XVII collagens

* AD, autosomal dominant; AR, autosomal recessive; XD, X-linked dominant; XR, X-linked recessive; ND, not determined.

† Most cases involve abnormalities in the elastic fibers, and in some cases, mutations in the elastin gene (ELN) have been disclosed. Occipital horn syndrome, a copper deficiency syndrome, allelic to the Menkes' syndrome gene (MNK-1), was previously known as X-linked cutis laxa and also Ehlers-Danlos syndrome IX (see Chap. 154).

‡ For detailed discussion on these genes, see Refs. 4 and 87.

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- *Epidermal melanin unit*: each melanocyte secretes melanosomes into a set number of keratinocytes (approximately 36)
- Differences in skin pigmentation are due to differences in size and distribution of melanosomes
 - Dark = small and single melanosomes
 - Light = small and grouped melanosomes
- Four stages of melanosome development
 - Stage I—premelanosome
 - ▲ Round in shape
 - ▲ No organized structure
 - Stage II—melanosome
 - ▲ Few filaments present
 - Stage III—melanosome
 - ▲ Eumelanosomes with oval, lamellar structure
 - ▲ Pheomelanosomes with round, irregular structure
 - ▲ Start of melanin deposition
 - ▲ Tyrosinase activity
 - Stage IV—melanosome
 - ▲ Partially melanized
 - ▲ Decrease in tyrosinase activity
 - ▲ Acid phosphatase present

TABLE 28-7 Clinical Features, Histopathology, Inheritance, Associated Biochemical Findings, and Predisposing Clinical Conditions in Cutaneous Diseases With Elastic Fiber Abnormalities*

Disease	Inheritance [†]	Clinical Manifestations	Histopathology of Skin	Biochemical Findings [‡] Related to Elastic Fibers and Predisposing Clinical Conditions
Pseudoxanthoma elasticum	AR, sporadic [§]	Yellowish papules coalescing into plaques Inelastic skin Cardiovascular and ocular abnormalities	Accumulation of pleiomorphic and calcified elastic fibers in the mid-dermis	Deposition of calcium apatite crystals, excessive accumulation of glycosaminoglycans on elastic fibers; D-penicillamine treatment; mutations in the ABCC6 gene
Buschke-Ollendorf syndrome	AD	Dermatofibrosis lenticularis disseminata and osteopoikilosis	Accumulation of interlacing elastic fibers in the dermis	Increased desmosine content in the skin
Cutis laxa	AR, AD, or NH	Loose, sagging, inelastic skin Pulmonary emphysema Tortuosity of aorta Urinary and gastrointestinal tract diverticuli	Fragmentation and loss of elastic fibers	Decreased desmosine content and reduced elastin mRNA levels; increased elastase activity in some cases; D-penicillamine treatment, inflammatory and urticarial skin lesions (e.g., drug reaction); mutations in the ELN or FBLN5 gene in limited cases
DeBary syndrome	AR	Cutis laxa-like skin changes Mental retardation Dwarfism	Rudimentary, fragmented elastic fibers	Reduced elastin mRNA levels
Wrinkly skin syndrome	AR	Decreased elastic recoil of the skin Increased number of palmar and plantar creases	Decreased number and length of elastic fibers	
Mid-dermal elastolysis	NH	Fine wrinkling of the skin, primarily in exposed areas	Fragmentation and loss of elastin in the mid-dermis	Inflammatory; sun-exposure related
Anetoderma	NH	Localized areas of atrophic, saclike lesions	Loss and fragmentation of elastic fibers in the dermis	Reduced desmosine content in the lesions; often secondary to inflammatory lesions

Continued

TABLE 28-7 (Continued)

Disease	Inheritance [†]	Clinical Manifestations	Histopathology of Skin	Biochemical Findings [‡] Related to Elastic Fibers and Predisposing Clinical Conditions
Elastosis perforans serpiginosa	NH	Hyperkeratotic papules, commonly on the face and neck	Accumulation and transepidermal elimination of elastic fibers	D-Penicillamine-induced abnormalities in elastin cross-linking
Elastoderma	Unknown	Loose and sagging skin with loss of recoil	Accumulation of pleiomorphic elastotic material without calcification in the mid- and lower dermis and the subcutaneous tissue	
Isolated elastomas	NH	Dermal papules or nodules	Accumulation of thick elastic fibers in the dermis	
Elastofibroma dorsi	NH	Deep subcutaneous tumor, usually on subscapular area	Accumulation of globular elastic structures encased in collagenous meshwork	Trauma on the lesional area
Actinic elastosis	NH	Thickening and furrowing of the skin	Accumulation of irregularly thickened elastic fibers in upper dermis	Chronic sun exposure
Marfan's syndrome	AD	Skeletal, ocular, and cardiovascular abnormalities, hyperextensible skin; striae distensae	Fragmentation of the elastic structure in the aorta	Mutations in the FBN1 gene Fibrillin 1 protein
Congenital contractural arachnodactyly	AD	Camptodactyly and joint contractures		Mutations in the FBN2 gene Fibrillin 2 protein
Williams syndrome	AD	Supravalvular aortic stenosis; velvety skin; dysmorphic facies	Disruption of smooth muscle and matrix relationship affecting blood vessels	Allelic deletion of the ELN gene; contiguous gene deletion syndrome

*Most of these conditions represent a group of diseases with clinical, genetic, and biochemical heterogeneity.

[†]AD, autosomal dominant; AR, autosomal recessive; NH, not a heritable disease.

[‡]The biochemical abnormalities have been demonstrated in only a limited number of patients in each group, and it is not known whether the biochemical changes are the same in each patient with given disease.

[§]Rare cases with a distinct acquired form of pseudoxanthoma elasticum have been described.

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TABLE 28-8 Glycosaminoglycans

Glycosaminoglycan	Distribution and Collagen Interaction
Hyaluronic acid	Found in dermis, umbilical cord, synovial fluid, cartilage, vitreous No interaction with collagen High levels associated with nonscarring wound healing (i.e., fetal)
Dermatan sulfate	Found in structures formed by collagen fibers; dermis, tendon, ligaments, heart valves, arteries, fibrous cartilage Interaction with type I collagen Decorin—small dermatan sulfate, found along surface of collagen fibrils and assist with lateral fibrils into fibers; low levels in hypertrophic scars
Chondroitin 4- to 6-sulfate	Hyaline and elastic cartilage, arterial medial layer, nucleus pulposus Interact with type II collagen
Heparan sulfate	Basement membrane, structures with reticular fibers: smooth muscle, liver, spleen nerves Interact with type III collagen

- ▲ Complete melanization
 - ▲ Very little tyrosinase activity
 - ▲ Acid phosphatase present
- Pathway of melanin formation
 - Melanosome structure is formed within melanocytes
 - Tyrosinase enzyme necessary for melanin formation is formed from Golgi apparatus of melanocyte
 - Tyrosinase is transported to melanosome and begins melanin formation
 - Melanosome is transferred to keratinocyte
 - Melanosome is degraded during ascent to cornified layer
 - Melanin is ultimately removed with loss of stratum corneum
- Melanin
 - Pigment that absorbs UV and visible light over a wide range of wavelengths without a distinct peak of absorption
 - Able to absorb free radicals
 - Tyrosinase is the main enzyme for melanin formation and catalyzes the first step: hydroxylation of tyrosine to dopa
 - Tyrosinase is copper-dependent
 - Tyrosine → dopa → dopaquinone: both these steps are catalyzed by tyrosinase
 - The type of melanin produced depends on presence of other factors
 - Eumelanin—brown-black pigment
 - ▲ Formed if divalent cations are present with dopaquinone
 - ▲ Found in dark, oval melanosomes
 - Pheomelanin—yellow-red pigment
 - ▲ Formed if cysteine (or glutathione) is present with dopaquinone
 - ▲ Found in round, lamellar melanosomes

- Control of melanin production
 - Pigmentation is either constitutive (level of pigment determined genetically) or facultative (inducible by UV exposure, “tan”)
 - Stimulated by melanocyte-stimulating hormone (MSH), which is derived from the larger precursor proopiomelanocortin (POMC); POMC is also the precursor for adrenocorticotropic hormone (ACTH); this explains the hyperpigmentation of Addison’s disease
 - Stimulated by estrogens and progesterones
- Melanocytic protein associated conditions: (see Chapter 9: Pigmentary Disorders)

ENDOTHELIAL CELLS

- Flattened epithelial-like cells
- Thickness < 10 μm
- Usually form a continuous monolayer with gap junctions between cells
- Endothelial cells rest on a basal lamina of laminin 1, collagens, fibronectin, nidogen (entactin), and heparan sulfate
- Endothelial cells have a polarized structure with differences between apical (lumen) aspect and basal surface
 - Integrin receptors for ground substance/matrix molecules on basal surface
 - Leukocyte receptors on apical (lumen) side
- Endothelial cells have a number of specialized structures
 - Weibel-Palade bodies (WPBs)
 - Contain von Willebrand factor (vWF), P selectin, and CD 63:
 - ▲ P selectin (CD62P) mediates leukocyte adhesion

- ▲ CD 63 is a lysosomal membrane glycoprotein that interferes with neutrophil adhesion
- vWF: amino acid protein; one specific domain binds to factor VIII, other domains perform other specific functions
- Fenestrae
 - Sieve-plate structure of membrane
 - 175 nm in diameter
 - Unique to endothelial cells
 - Capillaries composed of endothelial cells with fenestrae are more permeable to water and small-molecular-weight solutes
 - Located in capillaries in lymph nodes, renal glomerulus, intestine, hepatic sinusoids, and bone marrow sinusoids
 - Negative charge of fenestrae prevents transfer of negatively charged plasma proteins
- Caveolae
 - “Little caves” or vesicles associated with the plasma membrane via the protein caveolin
 - Serve as storage compartments for growth factor receptors structural components
- Tight (occludens) junctions
 - Provide dual function of sealing off paracellular space and dividing the cell into distinct apical and basolateral segments
 - Appear as continuous interlocking beltlike strands that associate laterally with tight junctions of adjacent cell
 - Consist of transmembrane proteins occludin and claudins
 - Also associated with cytoplasmic proteins ZO-1, ZO-2, and ZO-3
- Adherens junctions
 - Composed of cadherin adhesion molecules
 - Presence of junctions regulates paracellular transport and adhesion of molecules to one another
 - Cadherins link adjacent cells via a cytoplasmic plaque structure connected to the cytoskeleton
 - The plaque is composed of transmembrane proteins cadherin 5 (CD 144) and PECAM 1 (CD31)
 - Cadherin 5 is now renamed *vascular endothelial cadherin* (VE cadherin)
 - The cadherins are attached to the actin cytoskeleton by catenins
- Gap junctions
 - Clusters of transmembrane channels formed by six connexin monomers
 - Connexin 37, 40, and 43
 - Allow direct exchange of ions and small molecules between endothelial cells
- Complexus adherentes
 - Endothelial cells have no desmosomes
 - However, the desmosomal protein desmoplakin is located to complexus adherents and participates in a distinct type of cell contact separate from desmosomes
- Endothelial cells play a critical role in cutaneous inflammation
 - Endothelial cells produce a number of cytokines
 - IL-1
 - ▲ Responsible for upregulation of ICAM-1, VCAM-1, and E-selectin
 - ▲ Induces platelet-activating factor, prostaglandins, and nitric oxide
 - ▲ Activates T cells, serves as chemoattractant for lymphocytes, and stimulates proliferation of B cells
 - IL-6: has few effects on normal endothelium but plays a critical role as a growth factor for Kaposi sarcoma neoplasms
 - IL-8: likely plays a role as a chemoattractant for inflammatory cells
 - G-CSF
 - M-CSF
 - GM-CSF
 - Endothelial cells express a variety of adhesion molecules that play a vital role in inflammation
 - ICAM-1 (binds LFA-1 on leukocytes)
 - ICAM-2 (binds LFA-1 on leukocytes)
 - E-selectin (binds memory T cells, especially in chronic inflammation)
 - P-selectin (binds Lewis X, which is important in initial binding of PMNs to endothelium)
 - VCAM-1 (binds $\alpha 4\beta 1$ integrin of leukocytes)
 - MHC I, II (bind CD8 and CD4 on T cells)
 - LFA-3 (binds CD2 on T cells)
 - CD 44 (binds hyaluronic acid)

SWEAT GLANDS: ECCRINE AND APOCRINE

- Eccrine glands
 - Primary function of the eccrine unit is thermoregulation: cooling effects of evaporation of sweat on the skin surface
 - Highest density of eccrine glands is seen on the palms, soles, and axillae
 - Consists of two segments: secretory coil and a duct
 - Coil: composed of three distinct cell types: clear (secretory), dark (mucoid), and myoepithelial cells
 - Duct: outer ring of peripheral cells (basal) and an inner ring of luminal cells (cuticular); the coiled duct (proximal) is more active than the distal (straight) portion

- Duct is referred to as the *acrosyringium* because it spirals through the epidermis and opens directly onto the skin surface
- Eccrine sweat is produced via merocrine secretion in the coiled gland and is composed of water, sodium, potassium lactate, urea, ammonia, serine, ornithine, citrulline, aspartic acid, heavy metals, organic compounds, and proteolytic enzymes
- Stimulation of eccrine sweat production is mediated predominantly through postganglionic C fiber production of acetylcholine
- Apocrine sweat gland
 - Outgrowths of the superior portions of pilosebaceous units
 - Respond mainly to cholinergic stimuli
 - It consists of a coiled gland in the deep dermis or at the junction of the dermis and subcutaneous fat and a straight duct that traverses the dermis and empties into the isthmus (uppermost portion) of a hair follicle
 - Secretion is decapitation, a process where the apical portion of the secretory cell cytoplasm pinches off and enters the lumen of the gland
 - Sweat consists mainly of sialomucin; although odorless initially, as apocrine sweat comes in contact with normal bacterial flora on the surface of the skin, an odor develops
 - Specialized variants: the Moll's glands seen on the eyelids, the cerumen (ear wax-producing) glands of the external auditory canal, and the milk-producing glands of the breasts
 - Fox Fordyce disease
 - Chronic pruritic disease
 - Usually in women
 - Characterized by small follicular papular eruptions in apocrine areas
 - Caused by obstruction and rupture of intraepidermal apocrine ducts
- Apoeccrine sweat gland
 - Readily distinguished from classic eccrine and apocrine glands
 - Develop during puberty from eccrine-like precursor glands and are found in as many as 50% of the axillary glands in patients with hyperhidrosis
 - Long duct, opens onto skin surface (similar to eccrine glands)
 - Cholinergic and adrenergic, secretory rate is 10 times that of the eccrine glands because of its large glandular size
 - Thick segment of the duct is similar in morphology to apocrine glands
- Disorders of the eccrine glands and apocrine glands
 - Hyperhidrosis, or excessive eccrine sweat secretion
 - Localized hyperhidrosis of the palms and soles is often due to emotional stressors
 - Hypohidrosis: decreased eccrine sweating; anhidrosis: absent sweating seen in hereditary disorders such as the ectodermal dysplasias or in acquired conditions such as heat stroke or heat exhaustion
 - Miliaria crystalline: Excessive heat and humidity causes duct obstruction within the stratum corneum, asymptomatic superficial vesicles, and no surrounding inflammation
 - Miliaria rubra (prickly heat): Obstruction is found deeper in the epidermis; pruritic or tender red macules or papules that are often located on the thorax and neck
 - Miliaria profunda: duct obstruction at or below the dermal-epidermal junction; asymptomatic skin-colored papules
 - Apocrine miliaria: Inflammation follows intraepidermal rupture of apocrine ducts
 - Hidradenitis suppurativa: intense inflammation owing to follicular obstruction
 - Syringomas: most common benign sweat gland tumor; skin-colored papules on lower eyelids of adults

MATRIX METALLOPROTEINASES

- Group of zinc-dependent enzymes (endopeptidases) that degrade varying components of the extracellular matrix in both normal and diseased tissue
- Includes collagenases, gelatinases the stomelysins, the matrilysins, metalloelastases, enamelysins, and the membrane-type matrix metalloproteinases (MMPs) (Table 28-9)
- Synthesized as inactive proenzymes; limited proteolysis or treatment with an organomercurial compound sets up a chain of events causing conversion to the fully active form by complete removal of a propeptide (gelatinase A, MMP-2, can only be activated by the second mechanism)
- Cells secrete extracellular matrix (ECM) metalloproteinases in a complex pattern of response to multiple growth factors and oncogenes
- SCCs can secrete MMP-13 (collagenase-3), which preferentially cleaves type II collagen and gelatin, mediating their invasiveness
- Tissue inhibitors of metalloproteinases (TIMPs) are considered to be the major tissue inhibitors; these are secreted proteins that are tightly regulated during tissue remodeling and physiologic processes
- Inhibitors can modulate proteolysis once proenzymes have been activated
- α_2 -Macroglobulin, a nonspecific antiproteinase, accounts for more than 95% of the inhibitory activity

TABLE 28-9 Matrix Metalloproteinases

Enzyme	MMP Number	Alternate Name	Proenzyme Mol. Wt.	Known Matrix Substrates
Interstitial collagenase	MMP-1	Type 1 collagenase	52,000	Collagens I, II, III, VII, VIII, X, entactin, tenascin, aggrecan, denatured collagens, IL-1 β , myelin basic protein, L-selectin
Neutrophil collagenase	MMP-8		75,000	Collagens I, II, III, V, VII, VIII, X, gelatin, aggrecan, fibronectin
Collagenase-3	MMP-13		52,000	Collagens I, II, IV, IX, X, XIV, aggrecan
Gelatinase A Gelatinase B	MMP-2 MMP-9	72-kDa type IV collagenase 92-Kda type IV collagenase	72,000 92,000	Denatured collagens, collagens IV, V, VII, X, XI, XIV, collagen 1, species-dependent, elastin, fibronectin, laminin, aggrecan, myelin basic protein Denatured collagens, collagens IV, V, VII, X, XIV, elastin, entacin, aggrecan, fibronectin, osteonectin, IL-1 β , plasminogen, myelin basic protein
Stromelysin-1	MMP-3	Proteoglycanase	57,000	Proteoglycan core protein, laminin, fibronectin collagens I, IV, V, IX, X, XI, gelatin, elastin, tenascin, aggrecan, myelin basic protein, entactin, decorin, osteonectin
Stromelysin-2	MMP-10	Transin-2	55,000	Proteoglycan core protein, collagens III, IV, V, laminin, fibronectin, elastin, aggrecan
Stromelysin-3	MMP-11		61,000	α 1 Proteinase inhibitor
Matrilysin	MMP-7	PUMP Matrilysin-1	28,000	Collagen IV, denatured collagens, laminin, fibronectin, elastin, aggrecan, tenascin, myelin basic protein
Matrilysin-2	MMP-26	Endometase	28,000	Gelatin, α 1 proteinase inhibitor
Membrane type matrix metalloproteinase-1	MMP-14	MT1-MMP	63,000	Progelatinase A, denatured collagen, fibronectin, laminin, vitronectin, entactin, proteoglycans
Membrane type matrix metalloproteinase-2	MMP-15	MT2-MMP	72,000	Progelatinase A
Membrane type matrix metalloproteinase-3	MMP-16	MT3-MMP	64,000	Progelatinase A
Membrane type matrix metalloproteinase-4	MMP-17	MT4-MMP	70,000	Unknown
Membrane type matrix metalloproteinase-5	MMP-24	MT5-MMP	73,000	Progelatinase A

TABLE 28-9 (Continued)

Enzyme	MMP Number	Alternate Name	Proenzyme Mol. Wt.	Known Matrix Substrates
Membrane type matrix metalloproteinase-6	MMP-25	MT6-MMP	63,000	Unknown
Metalloelastase	MMP-12		54,000	Elastin, collagen IV, vitronectin, plasminogen, laminin, entactin, fibrinogen, fibrin, fibronectin
Enamelysin	MMP-20		54,000	Amelogenin, aggrecan
MMP-19	MMP-19	RASI-1	57,000	Gelatin, aggrecan, fibronectin
MMP-21	MMP-21		Unknown	Unknown
MMP-22	MMP-22		Unknown	Unknown
MMP-23	MMP-23		44,000	Unknown
Epilysin	MMP-28		56,000	Unknown

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HAIR DEVELOPMENT

See Chapter 1: Hair Findings.

NAIL DEVELOPMENT

See Chapter 3: Nail Findings.

QUIZ

Questions

- Renewal of the epidermis takes approximately:
 - 13–14 days
 - 1–14 days
 - 14–26 days
 - 26–28 days
 - 28–32 days
- Fibulin-2 is capable of binding
 - Fibrinogen
 - Versican
 - Aggrecan
 - All of the above
 - None of the above
- Stratum lucidum is a layer present between the granular and cornified layer found in:
 - Palmoplantar skin
 - Mucosa
 - Nail
 - Axillary skin
 - Scalp skin
- Seventy percent of the cornified cell envelope consists of:
 - Profillagrin
 - Loricrin
 - Involucrin
 - Filaggrin
 - Keratin
- Krause end bulbs or mucocutaneous end organs are found in:
 - Mucocutaneous junction
 - Hands and soles
 - Nipples/areola
 - Scalp skin
 - Nail apparatus
- Which is the only protein known to be present in both desmosomes and adherens junctions:
 - Desmplakin
 - Integrin
 - Desmocollins
 - BP antigen 2 (180kd)
 - BP antigen 1 (230kd)

7. The postganglionic neurotransmitter mediating eccrine sweat production is:
 - A. Acetylcholine
 - B. Epinephrine
 - C. Dopamine
 - D. Norepinephrine
 - E. Serotonin
8. Matrix metalloproteinases can be upregulated during normal development and physiologic tissue repair. Under pathologic conditions, squamous cell carcinomas can secrete:
 - A. Collagenase-1
 - B. Stromelysin-3
 - C. MMP-13
 - D. Gelatinase-9
 - E. Matrilysin-2
9. Which type of collagen is found in cartilage?
 - A. I
 - B. III
 - C. XI
 - D. XV
 - E. XVII
10. At what week of development do neural crest derived melanocytes produce melanin?
 - A. 8th week
 - B. 10th week
 - C. 12th week
 - D. 16th week
 - E. 18th week

Answers

1. D. It takes 13–14 days for maturation of keratinocytes from the basal layer to the corneum and another 13–14 days for shedding.
2. D. Fibulins are calcium-binding extracellular matrix proteins that do not form large aggregates but are capable of joining other supramolecular structures. Fibulin-2 is capable of binding fibrinogen, fibronectin, nidogen, proteoglycans, aggrecan, and versican.
3. A. The layer appears as an electronlucent zone and contains nucleated cells.
4. B. Loricrin accounts for the majority of proteins in the cornified cell envelope. It is insoluble and is highly hydrophobic. It is cross-linked by transglutaminase-3 to form homodimers and heterodimers with other proteins to increase solubilization.
5. A. These structures are found at the vermilion border of the lips, glans penis, and clitoris.
6. A. Desmoplakin bind intermediate filaments at their carboxy-terminal site. In adherens junctions, the N-terminus of desmoplakin can bind plakoglobin and plakophilin and in desmosomes, it can bind plakoglobin, plakophilin, and desmocollin.
7. A. Eccrine glands are highest in density in the palms, soles, and axillae. They are principally mediated by cholinergic stimulation.
8. C. Invasive SCCs can secrete MMP-13 (collagenase-3) which preferentially cleaves type II collagen and gelatin.
9. C. Many types of collagens can be found in cartilage including collagen II, IX, X, XI, XII, and XIV.
10. C. At the 8th week of fetal development melanocytes develop from the neural crest cells. It is not until the 12th week that melanocytes begin synthesis of melanin beginning in the head region.

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BIOSTATISTICS

ALICE CHUANG
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VARIABLE

- In a clinic study, the outcome may or may not be a number, for example, the “success” or “failure” of a drug treatment. However, we often want to represent outcomes as numbers
- A random variable is a function that associates a unique numerical value with every outcome of a study. The value of the random variable will vary over time or vary from individual to individual
 - There are two types of random variable—discrete and continuous
 - A random variable has either an associated probability distribution (discrete random variable) or probability density function (continuous random variable)

BINOMIAL DISTRIBUTION

- The binomial distribution is the discrete probability distribution of the number of successes in a sequence of n independent “yes/no” or “success/failure” outcome of an individual, each of which yields “Yes” or “Success” with probability p

NORMAL (GAUSSIAN) DISTRIBUTION

- The normal distribution, also called the Gaussian distribution, is an important family of continuous probability distributions, applicable in many fields. It can be:
 - Graphically categorized by a bell-shaped curve (Fig. 29-1)
 - The most frequently occurring value is in the middle of the range, and other probabilities tail off symmetrically in both directions
 - The mean and median are identical

- The probability that a measurement will fall within 1.96 standard deviations of the mean is 0.95
- Many statistical tests rely on the assumption that analyzed data are derived from a population that has a normal (Gaussian) distribution. Regression, correlation, t tests, and analysis of variance all depend on a normal distribution assumption

STATISTICAL ANALYSIS

Descriptive Statistics

- Descriptive statistics are used to describe the basic features of the data in a study. They provide simple summaries about the study variables, such as central tendency, variability, skewness, kurtosis, and associations of variables

CONTINUOUS VARIABLE

- Central tendency
 - Mean
 - Arithmetic average = sum of all the values divided by the number of observations
 - Outliers weigh heavily on the mean but it does provide a central value representative of the entire collection of numbers
 - Median
 - Middle value of a set of data; where 50% of the values are below this point, and 50% of the values are above it
 - It provides a central value that is not influenced by high and low extremes in the data
 - Mode
 - Represents the value occurring most frequently in a data set
 - A data set has no mode when all the values appear in the data with the same frequency. A data set has multiple modes when two or more values appear with the same frequency

- Variability
 - Variance
 - A measure of the spread or variability of a distribution
 - Variance [$V(X)$ or σ^2] equals the average value of the squared difference between measurements and their mean
 - Variance is small if many data points are close to their mean and is zero if all data points are equal
 - Variances are typically useful only when the measurements follow a normal or at least a symmetric distribution
 - Standard deviation (SD)
 - The standard deviation, also called the root-mean-square deviation, is equal to the square root of the variance
 - It is also a measure of the spread of a distribution and has the same measuring scale as the random variable
 - Standard deviation has a simple interpretation only if the distribution of the random variable is Gaussian (normal), the 95% of the outcomes is expected to be within 2 standard deviations of the mean; the 68% of outcomes is within 1 SD, and 3 SDs holds 99.7% of values (see Fig. 29-1)
 - Standard error of mean (SEM)
 - The standard deviation of sample mean is called standard error of mean (SEM)
 - Sample mean is an arithmetic average of set of samples. It is a random variable which has a distribution with the same mean as the samples and the standard deviation equal to standard deviation (SD) of samples divided by squared root of sample size
 - Standard error of mean falls as the sample size increases
 - Standard error of mean increases as standard deviation increases
- Standard deviation versus standard error of mean: how widely scattered some measurements are versus evaluation of the accuracy around the estimate of the mean measurement
- Range
 - A smallest length contains all the data
 - Range = largest measurement – smallest measurement
- Skewness
 - Positively skewed data are represented by a distribution that has a long right tail while Negatively skewed data are represented by a distribution that has a long left tail (Fig. 29-1)
- Kurtosis
 - Positive when the tails are narrow with a steep peak and is negative when the data distribution curve has wide tails with a flat peak
- Association
 - Correlation coefficient
 - Measures how related two values are
 - The range of the coefficient is -1 to $+1$
 - The strength of the relationship between two variables is determined by how far the correlation coefficient is from zero (absolute value)
 - Zero equals no association, $+1$ equals a perfect positive correlation, and -1 equals a perfect negative correlation

DISCRETE VARIABLE

- Frequency
 - The number of times the event occurred in a study
- Probability and percentage
 - A number, between 0 and 1, that indicates how likely an event is to occur on the basis of the number of events per the number of trials
 - Probability (p) = frequency/total number of trials
 - Percentage = $p \times 100$

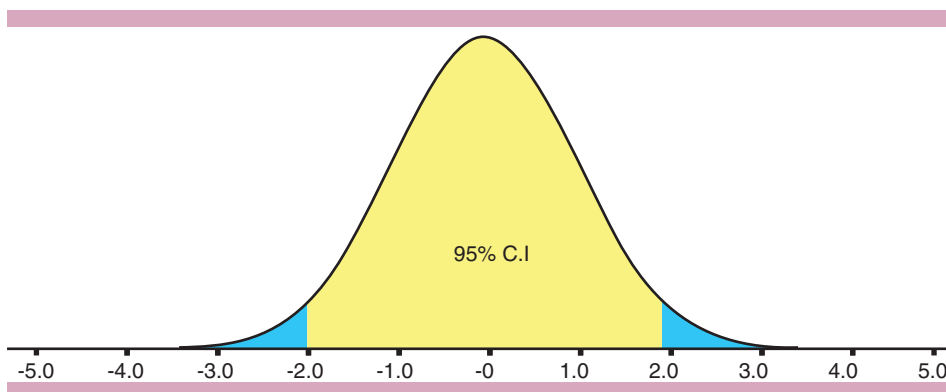


FIGURE 29-1 A graph showing significance interval.

- Odds
 - Ratio of the probability of an event occurring (p) to the probability of the event not occurring ($1-p$)
 - Odds = $p / (1-p)$
- Odds ratio
 - The ratio of the odds of an event occurring in one group to the odds of it occurring in another group
 - These groups might be control and treated, or any other two groups classification
 - If the probabilities of the event in each of the groups are p_1 (first group) and p_2 (second group), then the odds ratio is:

Confidence Interval (Fig. 29-1)

- Estimated range of values which is likely to include an unknown population parameter
- The probability that the confidence interval produced will contain the true parameter value is through the selection of a confidence level for an interval
- Common choices for the confidence level are 0.90, 0.95 (most commonly used), and 0.99
- If the 95% confidence limits for an unknown quantity are $[a; b]$, then 95% of similarly constructed confidence limits in repeated samples from the same population would contain the unknown quantity
- Therefore, there is 95% confidence that the unknown value is in the interval $[a; b]$
- Decreasing the level of confidence, results in a decrease in the size of the corresponding interval
- Increasing the sample size will decrease the length of the confidence interval without reducing the level of confidence

Hypothesis Testing (Table 29-1)

NULL HYPOTHESIS (H_0)

- The assumption that there is no difference in parameters (mean, ratio, variance, etc.) between two or

more entities represents a theory that has not been proven

- Any observed difference in samples is due to chance or sampling error, while the alternative hypothesis asserts that there is a significant systematic association
- Assumes that a hypothesis may not be correct (i.e., no effect of a treatment) and attempts to gather evidence against that assumption (i.e., tries to reject H_0 and accept the alternative hypothesis)
- Statisticians often use H_0 to indicate the statistical hypothesis being tested

TYPE I ERROR (ALPHA)

- In hypothesis testing, rejecting the null hypothesis when it is in fact true; results in a false positive study,
- For example, the testing result from observed data shows a difference where the true difference (unobservable) does not exist
- Probability of a type I error: $P(\text{type I error}) = \text{significance level} = \alpha$
- Alpha level is the probability of a type I error; the significance is usually set at 0.05

TYPE II ERROR (BETA)

- In hypothesis testing, failing to reject a false null hypothesis; results in a false-negative study that rejects a true alternative hypothesis
- For example, a study shows that no difference exists when in fact it does
- Probability of a type II error: $P(\text{type II error}) = \beta$
- May occur when the sample size is too small [it always occurs, but you can control (minimize) it by increasing sample size]
- Type I and type II errors are inversely related; for any set of data, the smaller the risk of one, the higher the risk of the other. In general, we fix the

TABLE 29-1 Understanding Hypothesis Testing*

Study Results	Reality	
	Treatments Are Really Not Different	Treatments Are Really Different
Treatments are <i>not</i> different	Correct decision (probability = $1 - \alpha$)	Type II error (probability = β)
Treatments <i>are</i> different	Type I error (probability = α)	Correct decision (probability = $1 - \beta$) (power)

*Note: Only pertains to outcomes of a randomized controlled trial.

probability of type I error and minimize the type II error by increasing sample size

Power (Pw)

- Definition: probability of finding a significant association if one truly exists (probability that the test will reject a false null hypothesis)
- $1 - \text{Beta} = Pw$ (therefore, as the power increases, the chances of a type II error decreases)
- Power is commonly set at 80 or 90%; maximum power a test can have is 1, the minimum is 0. The goal of a study is to have the power as close to 1 as possible
- The power of a study depends on: alpha, beta, effect size (small effect size decreases the power), and sample size (a small sample size, decreases the power of a study). The power is also affected by variance (large variance, decreases power of a study)

Diagnostic Performance (Table 29-2)

- A diagnostic test can result in the following outcomes:
 - *True positive*: the test is positive and the disease is present
 - *False positive*: the test is positive and the disease is absent
 - *True negative*: the test is negative and the disease is absent
 - *False negative*: the test is negative and the disease is present

Test Sensitivity

- General: assesses the validity of a test
- Definition: the ability of a screening test to identify correctly those who *have* the disease: $\text{True positive} / (\text{True positive} + \text{False negative})$
- Properties: a test with high sensitivity has few false-negative results, independent of disease prevalence in the community

Test Specificity

- General: assesses the validity of a test
- Definition: the ability of a screening test to identify correctly those who *do not have* the disease: $\text{True negative} / (\text{True negative} + \text{False positive})$
- Properties: a test with high specificity has few false-positive results, independent of disease prevalence in the community

Positive Predictive Value (PPV)

- General: assesses the reliability of a positive test
- Definition: the probability that a patient has a disease when the test for the disease is positive: $\text{PPV} = \text{True positive} / (\text{True positive} + \text{False positive})$
- Properties
 - Affected by two factors
 - Disease prevalence: higher disease prevalence results in a higher PPV
 - Specificity (only when disease is infrequent): higher specificity results in a higher PPV (with infrequent diseases)

Negative Predictive Value (NPV)

- General: assesses the reliability of a negative test
- Definition: probability that the patient does *not have* disease when the results are negative: $\text{NPV} = \text{True negative} / (\text{True negative} + \text{False negative})$
- Properties
 - Affected by two factors
 - Disease prevalence: lower disease prevalence results in a higher NPV
 - Test sensitivity effect is minimized at a low prevalence and results in a more reliable negative test

Measures of Effect

- *Probability*: a number, between 0 and 1, that indicates how likely an event is to occur on the basis of the number of events per the number of trials
- *Odds*: ratio of the probability of an event occurring to the probability of the event not occurring
- $\text{Odds} = \text{probability} / (1 - \text{probability})$

Relative Risk or Risk Ratio (RR)

- Definition: ratio of the incidence of disease in exposed individuals to the incidence of disease in *non* exposed individuals
- Can be determined in a prospective cohort study
- Relative risk may be the same as odds ratio for small probabilities
- Meaning of results:
 - If $RR = 1$: there is no evidence for increased risk in exposed individuals compared with nonexposed individuals

TABLE 29-2 Calculating Sensitivity and Specificity

Test Results	Disease	
	+	–
+	A (TP)	B (FP)
–	C (FN)	D (TN)

Note: TN, true negative; FN, false negative; TP, true positive; FP, false positive; sensitivity = $TP / (TP + FN)$; specificity = $TN / (TN + FP)$.

- If $RR > 1$: the risk in exposed individuals is greater than the risk in nonexposed (i.e., there is a positive association)
- If $RR < 1$: the risk in exposed individuals is less than the risk in nonexposed (i.e., there is a negative association; suggests a “protective” effect)

Odds Ratio (OR) (Table 29-3)

- Used as a measurement in a retrospective case-control study
- Definition: Ratio of the odds of cases that have the disease to the odds that controls have the disease
- Measure of whether a certain *exposure* is associated with a specific disease
- The OR approximates the RR when
 - Cases studied are representative of people with disease in the population
 - Controls studied are representative of people without disease in the population
 - The disease being studied does not occur frequently

Statistics Equations Review

- Sensitivity = $A/(A + C)$
- Specificity = $D/(B + D)$
- PPV = $A/(A + B)$
- NPV = $D/(C + D)$
- Relative risk = $[A/(A + B)]/[C/(C + D)]$
- Odds ratio = $(A \times D)/(B \times C)$
- Attributable risk = $[A/(A + B)] - [C/(C + D)]$

P-Value (Probability Value)

- The level of statistical significance
- Alpha or type I error (incorrect rejection of the null hypothesis)
- Definition: probability that a difference between two groups could have arisen by chance alone; the estimated probability of rejecting the null hypothesis of a study question when that hypothesis is true
- Commonly set at 0.05: this means that the probability that the difference between the two groups occurred by chance alone was 0.05, or 1 in 20

TABLE 29-3 Calculating Odds Ratio

	Disease Develops	Disease Does Not Develop
Exposed	A	B
Not exposed	C	D
Note: $OR = AD/BC$.		

- The lower the *P*-value, the lower the chance that the difference occurred by chance alone as opposed to the intervention being tested

Outcomes Assessment

RELIABILITY

- Precision of a test
- Measures the reproducibility and consistency of a test
- Reduced by random error

TEST VALIDITY

- Accuracy of a test
- Measures the trueness of measurement
- Reduced by systematic error
- Types
 - *Internal validity*: a study with no major methodological problems thus minimizing the error in correctly finding a causal relationship between the experimental treatment and the observed effect
 - *Construct validity of cause*: infers that the observed effect is attributable to the specific experimental intervention and not other variables of effect; support for the intended interpretation of the variables
 - *External validity*: relates to the generalizability of the study. Could the observed effect be produced in other settings, beyond the studied populations and at other times?
 - *Statistical conclusion validity*: are the conclusions reached justifiable on statistical grounds? Does the effect generalize to the population from which the sample was drawn?

Study Design

MULTIVARIABLE MODEL/MULTIVARIATE ANALYSIS

- A model relating multiple predictor variables (risk factors, treatments, etc.) to a single response or dependent variable
- It is used to examine the relationship between a single response and a dependent variable and multiple predictor variables
- One can ascertain the relationship between a predictor variable and the dependent variable independently and account for the effects of other predictor variables

INTENTION TO TREAT

- Subjects are analyzed according to the treatment group to which they were assigned, even if they did not receive the intended treatment or received only a portion of it
- This analysis reflects real-world nonadherence to treatment

DISEASE INCIDENCE

- Number of *new* disease cases per population at risk
- The number of new disease cases in the population during a specific time divided by the number of individuals at risk of developing the disease during that specific time
- High incidence implies high disease occurrence
- Low incidence implies low disease occurrence
- Measured over a given time interval, data are usually obtained from a prospective cohort study
- Determines probability of developing a specific disease
- Used to detect etiologic factors

DISEASE PREVALENCE

- Number of *current* cases per population at risk: the number of current disease cases at a specific time divided by the number of individuals in the population at that specific time
- Old: persistent active disease contracted previously
- New: onset of active disease
- Point prevalence: disease prevalence at a point in time
- Period prevalence: disease prevalence over a given period of time
- Measures amount of illness in the community
- Determines health care needs of the community
- Data are usually obtained from a cross-sectional survey

RESEARCH ERROR

- Two types of research error
 - Random error: handled with the use of statistical tests and methods
 - Systematic error: uncontrolled error that may change the results and/or interpretation of research

SELECTION BIAS

- Nonrandom systematic error in the design or conduct of a study
- Types
 - Sampling bias: results from failure to ensure that all members of the reference population have a known chance of being selected for inclusion in the sample
 - Allocation bias: results from systematic differences in the characteristics of those assigned to treatment versus control groups in a controlled study
 - Selection bias: results when the following occurs: (1) self-selection of individuals to participate in a survey or experimental study; (2) selection of samples or studies by researchers to support a particular hypothesis

- Nonresponder bias: results if the survey results differ substantially from those that would have been generated if the response rate was 100%
- Interviewer bias: results from the personal prejudice of the individual conducting the interview.
- The following characteristics of studies can decrease bias: randomization (minimizes selection bias), blinding, matching. Prospective studies may decrease the chance of patient selection bias

CONFOUNDING

- Variable that has independent associations with both the *independent* (predictor) and *dependent* (outcome) variables
- Examples include gender, age, socioeconomic status, and co-morbidities

RANDOMIZATION

- Best means of avoiding allocation bias
- Balances the groups for prognostic factors (i.e., disease severity)
- Eliminates overrepresentation of any one characteristic within the study group
- Should be concealed from the clinicians and researchers of the study to help eliminate conscious or unconscious bias

BLINDING

- People involved in the study do not know which treatments are given to which patients
- With double blinding, neither the patient nor the clinician knows which treatment is being administered
- Eliminates bias and preconceived notions as to how the treatments should be working

SAMPLE SIZE

- A sample is a subgroup of the population (population consists of every person who fits a given set of respondent criteria)
- Ideally the sample is selected randomly and is comparable with the population
- Inclusion criteria defines the survey's target population
- Specifications needed to estimate sample size in a randomized trial:
 - Differences in response rates to be detected
 - Estimate of the response rate in one of the groups
 - Level of statistical significance (alpha): the lower the significance level, the greater the required sample size
 - Level of power (1 - beta): the higher the power specification, the greater the required sample size
 - Whether test should be one- or two-tailed

- Large enough number needed to reject a null result (i.e., to be sure that there is some treatment effect)

“GOLD STANDARD”

- Provides objective criteria (e.g., laboratory test not requiring interpretation) or a current clinical standard (e.g., a venogram for deep venous thrombosis) for diagnosis

CLINICAL TRIALS

- The type of study design chosen for a clinical trial depends on the purpose of the study (Table 29-4)

Steps for Conducting Clinical Trials Include

- Defining a relevant research question
- Selecting instrumentation
- Selecting an appropriate study design and method for statistical analysis
- Determining sample size and sampling procedure

Characteristics of Clinical Trials

- Clinical trials are ideally performed in a controlled setting
- They may evaluate any of the following
 - New drugs
 - Medical devices
 - Biologics
 - Other interventions on patients
 - Safety and efficacy of an experimental therapy
 - Whether a new intervention is better than standard therapy and/or
 - The efficacy of two standard or marketed interventions
- Examples of various trials include
 - *Treatment trials*: involves test treatments for a specific disease, new combination of drugs or new approaches to surgery or radiation therapy
 - *Supportive care trials (quality-of-life trials)*: explores ways to improve comfort and the quality of life for individuals with a chronic illness

- *Prevention trials*: looks for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning
- *Screening trials*: includes the study of new ways of finding diseases or conditions in people who are at risk, before they have any signs or symptoms
- *Diagnostic trials*: these are conducted to find better tests or procedures for diagnosing a particular disease

Cost-Identification Studies

- Evaluation of the cost of providing treatments
 - Cost-effectiveness analysis
 - Evaluates the costs and clinical outcome
 - Results are reported as cost per clinical outcome
 - Cost-benefit analysis
 - Evaluation of costs and benefits of a specific treatment
 - Results are reported in monetary units
 - Cost-utility analysis
 - Evaluation of cost and utility of a specific treatment
 - Results are reported as cost per quality-adjusted life-year (QALY)

Experimental Design (Study Design) of Clinical Trials

- *Observational study*: investigator does not intervene in any way, but merely observes outcomes (case series, case-control studies, cross-sectional surveys, and cohort studies)
- *Survey study*: involves measuring a set of parameters in one pass through a sample of the population. Used for measuring frequency or magnitude of parameters, but can also be used to measure associations between variables. They can be repeated at time intervals and then combined to predict trends
- *Experimental study*: investigator intervenes in some way to effect the outcome, tests causal hypotheses where treatment can be given to patients. Biases include selection, informational, observer, and interviewer. The types include: simple experiment,

Table 29-4 Different Types of Study Designs

Usual Purpose of Study	Type of Study Design	Sampling Procedure/Type of Survey
Descriptive	Survey study	One that uses the sample population
Hypothesis generating	Observational study	Case control, cohort or cross sectional
Hypothesis testing	Experimental or observational studies	Clinical trials, case control, cohort, or cross sectional

repeated-measure, repeated measure with crossover, and factorial design)

Data Collection:

- *Retrospective study*: the events of interest transpired before the onset of the study,
 - May also be called “case-control” studies in which profiles of subjects in a particular “case” group (e.g., smokers) are compared with those in a control group that has been selected to be as similar as possible to the “case” group
 - There is a risk of investigator bias: investigator picks subjects that are most likely to show the effect that prompted the study in the first place
 - There is a risk of recall bias: subjects affected by the outcome are more likely to remember an exposure than those unaffected
- *Prospective study*: the direction of inquiry is forward from the cohort inception and evaluation of the events of interest transpire after the onset of the study, data collection forms are designed at the outset of the study, also known as “cohort studies”

Other Characteristics of Clinical Trials

- *Cross-sectional study*: used to survey one point in time
- *Longitudinal study*: follow the same patients over multiple points in time
- *Blinding*
 - Study subjects, anyone involved in the subject’s management, and those collecting and analyzing clinical data are unaware of the assigned treatment, in order to decrease bias
 - Takes into account the investigator’s or study subject’s influence of his/her belief in efficacy of treatment

Techniques

- Masking of the group to which the subject is assigned
- Simple blinding applies to subjects only
- Double blinding applies to the subject and investigator, open (non-blind) trials
- Blind evaluation (by a third party) when blinding cannot be achieved

Randomization

- Occurs when each patient has an equal chance, of being given each treatment, but the treatment to be given cannot be predicted
- Equalizes confounders, especially those that are unknown or immeasurable,
- The process may either involve random selection for inclusion or random allocation of treatment

Placebo

- Inert substance given to control subjects that are indistinguishable from the primary treatment, therefore, the only difference between groups is the specific intervention under study

Control Study

- Clinical study that includes a comparison (control) group which receives a placebo, another treatment, or no treatment at all compared to the study group

Sampling Procedure/Type of Surveys

RANDOMIZED CONTROLLED STUDY (PROSPECTIVE, EXPERIMENTAL)

- This type of trial has the following features
 - randomised allocation of participants to groups (treatment versus control)
 - blinding of the following: the participants to group allocation, the practitioner delivering the intervention, and/or the researcher assessing the outcome
 - use of a placebo control group
 - monitoring of the experimental conditions and interventions
- Also known as a parallel group design (“completely randomized”)
- Randomization is one of many components that help to reduce bias
- The goal is to decrease all possibilities for a difference in outcome to either the intervention or chance
- The likelihood that the intervention is the reason for a difference between groups (placebo versus treatment) depends on the level taken to indicate statistical significance (usually $P < 0.05$ or $P < 0.01$)
- Purpose of study can be characterized as either “explanatory” or “pragmatic”:
 - Explanatory approach: explains a biological principle
 - focus is efficacy: assessment of differences in effect between two or more conditions under ideal, highly controlled conditions
 - commonly have one specific outcome measure
 - Pragmatic approach: asks the question: “What is the better treatment in the particular clinical circumstances of the patients in the study?”
 - focus is effectiveness: assess differences in effect between two or more conditions when used in normal real-world clinical circumstances
 - not placebo controlled,
 - heterogeneous group of patients
- “Intention to treat” is a strategy for the analysis of randomised controlled trials that compares patients

in the groups to which they were originally randomly assigned; clinical effectiveness may be overestimated if an intention to treat analysis is not done

- *Repeated measure study* (prospective, experimental)
 - Used when significant baseline variation is expected. The outcome event is measured several times during the trial
- *Factorial design study* (prospective, experimental)
 - Evaluation of two interventions compared to a control in a single trial. Main disadvantage is the possibility of interaction and the diminution of the power of the trial. Therefore, a larger sample size is needed to compensate for the decrease in power

CASE-CONTROL STUDY (RETROSPECTIVE, OBSERVATIONAL)

- A group of individuals with the *condition/disease* (cases) and a group of people *without the condition* (controls) are identified
- Ideal study if the outcome is rare and/or the time period from exposure to outcome is long
- The effect of an individual's exposure to various factors is evaluated in terms of the development of the outcome/disease being studied
- Information is collected about past exposure to suspected etiological factors in the case and control individuals by looking at their records or by questioning
- Both reporting bias and diagnostic bias may arise in this type of study (bias occurs when there is a systematic difference between the true results and those that are observed in the study)
- Less reliable than randomized controlled trials and cohort studies because a statistical relationship does not mean that one factor necessarily caused the other
- Can only determine odds ratio (OR) of developing the condition
- *Case report* (retrospective study)
 - A report on a single patient
 - Reports of cases with no control groups with which to compare outcomes; they have no statistical validity
- *Case series* (retrospective study)
 - Noncomparative study looking at the effect of treatment of individual patients and presentation of interesting or unusual observations

COHORT STUDY (PROSPECTIVE OR RETROSPECTIVE, OBSERVATIONAL)

- Large groups of *exposed* and *nonexposed* individuals are followed for long periods of time, to provide information on a range of outcomes, including incidence of disease, death from disease and other rare adverse events
- Ideal study when the outcome is frequent or the latency period is short

- The fact that individuals are not allocated by chance is the main difference between cohort studies and control randomized trials
- Since there are differences in baseline characteristics between the intervention and comparison groups, cohort studies are subject to selection bias and confounding.
- Types of cohort studies
 - Concurrent (concurrent prospective or longitudinal): original population is defined at the start of the study, and subjects are followed through time and the individuals are evaluated to see if the disease does or does not develop
 - Retrospective cohort (historical cohort, nonconcurrent prospective): exposed population is defined by historical records, and outcome is determined at the time the study begins
- Types of comparisons in cohort study
 - Intervention versus alternative intervention
 - Intervention versus no intervention
- Relative risk (RR) is used to assess the effect of a risk factor in a cohort study

CROSSOVER TRIAL (PROSPECTIVE, EXPERIMENTAL)

- Each subject receives both treatments being compared or the treatment and control
- Since a disease or process needs to persist long enough for the subjects to be exposed to each of the experimental treatments, crossover trials are generally restricted to the study of short term outcomes in chronic diseases or processes
- A washout (no treatment) period between consecutive treatments will help diminish the main disadvantage of the crossover trial: that the effects of one treatment may "carry over" and alter the response to subsequent treatments

META-ANALYSIS (RETROSPECTIVE)

- Observational study of the evidence that combines information from different studies to derive an overall estimate of a treatment's effect
- Two issues exist with this type of study: (1) publication bias: an example is the possibility that studies showing an effect may be more likely to be published than studies showing no effect; (2) combinability of evidence due to varying quality and design of the studies being compared
- Uses statistical techniques to combine the results of several studies as if they were one large study

Phases of Clinical Trials

- There are four phases of clinical trials. Each phase can be viewed as an individual clinical trial
- The process of drug-development typically proceeds through all four phases, which could take several years

- Once a drug has passed the first three phases, it can be used by the general public
- Prior to the initiation of clinical trials on a drug, pharmaceutical companies will perform pre-clinical studies. The purpose of these studies is to evaluate efficacy, toxicity and pharmacokinetic data on the drug being studied
- Phase 0 (human microdosing studies)
 - Used to bring medications to the market faster based on data from preclinical studies
- Phase 1: Typically, first stage of testing in healthy human subjects (occasionally in patients with actual disease)
 - Objective is to obtain preliminary information on dosage, absorption, pharmacokinetics, pharmacodynamics, and the relationship between toxicity and the dose-schedule of treatment
 - Types of phase 1 studies:
 - *Single ascending dose (SAD)*
 - ▲ Pharmacokinetic data, for a certain dose of a drug, is evaluated in a group of patients for a period of time
 - ▲ If no adverse side effects occur, a new group of patients is given a higher dose
 - ▲ Dose escalation continues until a pre-calculated pharmacokinetic safety level is reached, or an unacceptable side effect results (which is the Maximum tolerated dose (MTD))
 - *Multiple ascending dose studies (MAD)*
 - ▲ Evaluates the pharmacokinetics and pharmacodynamics of various doses of a drug
 - ▲ A group of patients receives multiple low doses of the drug, with collection and analysis of blood and/or other fluids, at various time points
 - ▲ Escalation of the dose in subsequent groups occurs
- Phase 2: Evaluates efficacy and continues phase 1 safety assessments in groups of 100–300 individuals
 - Studies are occasionally divided into either phase 2A (to assess dosing requirement) or phase 2B (to study efficacy)
- Phase 3: Comparative trial that determines the effectiveness and safety of a new treatment relative to standard therapy
 - Randomized controlled multicenter trials on large patient group (1000–2000 or more)
 - Typically expected that there be at least two successful phase 3 trials
 - The last stage before product licensing
 - Other reasons for performing phase 3 trials include: “label expansion” (to show the drug works for additional types of patients/diseases beyond the original use for which the drug was

approved), obtain additional safety data, or to support marketing claims for the drug

- Phase 4: postmarketing studies of licensed products

Practice Guidelines

- Evidence-based developed statements to assist practitioners about appropriate health care for specific clinical circumstances
- Guidelines review and evaluate the evidence and then make explicit recommendations for practice
 - Safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population
 - Adverse effects detected by this phase may result in the withdrawal or restriction of the drug

Randomized Controlled Trials

- Study the effect of a therapy or test on patients with randomization and with large enough sample size to avoid confounding and selection bias
- Include methodologies that reduce the potential for bias and that allow for comparison between intervention groups and control groups (no intervention)
- Evidence for questions of diagnosis is found in prospective trials that compare tests with a reference or “gold standard” test
- From the results, an estimate of the number of patients who would need to be treated (NNT) to prevent one adverse outcome is calculated by:
- $NNT = 1 / (\text{Rate in untreated group} - \text{Rate in treated group})$
- NNT helps to estimate the effect that might be expected to be observed by using the new treatment or preventive measure but is limited by not taking into account quality of life

Systematic Reviews

- Focus on a clinical topic and answer a specific question
- Extensive literature searches are conducted to identify studies with sound methodology
- The studies are reviewed, assessed, and summarized according to the predetermined criteria of the review question

COMPARISON OF DATA

Analysis of Variance

- Used to determine if samples are actually from a single population
- Does not allow you to compare which groups are more likely to differ from the other (that’s the *t* test)

Intention-to-Treat Analysis

- All patients should be analyzed within the treatment group to which they were randomized in order to preserve the goals of randomization
- Minimizes nonresponder and transfer bias
- Statistical tests
 - Parametric tests are more likely to detect a difference if one exists
 - When using a parametric test, the following must be true: samples are obtained from a population that is normally distributed and that the sample variances are essentially equal
 - Nonparametric tests do not make any assumptions about the underlying distribution of the data; less powerful than parametric tests

t-Test

- Used to test for differences between the mean values of two treatment groups
- All *t*-tests are parametric tests
- Employs the statistic (*t*): *t* = difference between sample means/standard error of the difference in sample means (variability within groups)
- The larger the ratio, the more likely it is to demonstrate a statistical difference between the 2 groups

Chi-Square Test

- Used to determine if differences exist between observed and expected frequencies of results that are tabulated in a 2 × 2 contingency table
- Statistical test that consists of three different types of analysis
- Goodness of fit: determines if the sample under analysis was drawn from a population that follows some specified distribution
- Test for homogeneity: answers the proposition that several populations are homogeneous with respect to some characteristic
- Test of independence: tests the null hypothesis, which states that two criteria of classification, when applied to a population of subjects, are independent; if they are not independent, then there is an association between them

Correlation Analysis

- Evaluates the degree of association between two variables; the two variables are both treated equally, and neither is assumed to be the predictor or the outcome
- The null hypothesis for a correlations analysis is that the correlation coefficient is equal to zero (no relationship) or that variable 1 and variable 2 are not related

- Correlation coefficient (*r*): a statistical parameter quantifying the degree of association between the 2 variables

Regression Analysis

- Makes predictions of an outcome on one variable in relation to another variable based on the observed relationship between the variables
- The studied variables are either dependent (outcome) or independent (causative)
- Types of regression analysis: linear (most common), multiple, weighted, and logistic
- The assumptions for linear regression are that the dependent variable (*Y*) is adequately modeled as being linearly related to a single independent variable *X*

QUIZ

Questions

1. Your office has just purchased a new screening test for fungal infections. You decide to use the test along with the gold standard culture. Calculate the sensitivity and specificity of the test using the information below. What do these results mean to you?

Results of Screening Test	Fungal Infection	No Fungal Infection
Positive	25	1
Negative	2	100

2. You wish to find further information about this screening test. A trial has been performed in a clinic population similar to the one that you treat and produced the following results. Calculate the positive and negative predictive value of the test. What do these numbers tell you?

	Population		
Test Results	Fungal Infection	No Fungal Infection	Total
Positive	200	10	210
Negative	20	770	790
Total	220	780	1,000

3. Which is true for a normal (Gaussian) distribution?
 - A. The graph normally has 2 peaks
 - B. When the data are distributed normally, the mean and median are very close and may be identical
 - C. It only applies to cross-sectional trials
 - D. The most frequently occurring value is on either end of the curve
4. A study which is done in a very specific population that is not generalizable to the population that you treat, would be said have low:
 - A. Construct validity
 - B. Internal validity
 - C. External validity
 - D. Statistical validity
5. The results of a randomized controlled trial using a therapy to treat a severe skin malignancy showed a mortality rate of 18% in the untreated group and 5% in the treated group. Calculate the number needed to treat (NNT) to determine how many people would need to be treated in order to prevent one death.
6. When looking at the possible outcomes of a randomized controlled trial that compare two treatments, you generate a table based on your conclusions about treatment and what is the true outcome. Identify in the table, which would be a “correct decision,” “type II error,” and “type I error.” (Hint: two boxes are a “correct decision.”)

Your decision	Truth	
	Treatments are not different	Treatments are different
Treatments are not different	Correct decision	Type II error
Treatments are different	Type I error	Correct decision

7. The power of a test has the following qualities, EXCEPT:
 - A. It equals 1 – the probability of making a type II error
 - B. It is the probability of correctly concluding that the treatments do in fact differ
 - C. It is the probability of making a type I error
 - D. It can be expressed as $1 - \beta$
8. The dermatology consult records from a large university hospital from the year 1980, were examined

in 1999 to see if their recorded effects of a treatment was related to the development of lymphoma by 2002. This is an example of:

- A. A cross sectional study
 - B. A case control study
 - C. A concurrent cohort study
 - D. A retrospective cohort study
 - E. A randomized controlled trial
9. A study was conducted to assess the risk of stroke in relation to the use of an oral therapy that you wish to use for your patient. A standard questionnaire was administered to patients who were admitted with a stroke as well as to a control set of patients who were admitted for non-stroke related problems to determine their use of this medication. They found that 10 of the 70 patients who had a stroke took the medication and that of 1200 patients who did not have a stroke, 200 of those patients had a history of taking the medication. Calculate the odds ratio for these data.

	Cases With Stroke	Cases Without Stroke
History of medication	A 10	B 200
No history of medication	C 60	D 1000

10. What are characteristics of a phase 3 trial?
 - A. These are small studies intended to provide preliminary information on dosage, metabolism, toxicity and absorption
 - B. They involve fairly large comparative trials based on previous information from smaller trials to determine the effectiveness and safety of a new treatment relative to standard therapy
 - C. They only provide information on feasibility
 - D. They do not focus on generalizability to the population

Answers

1. Sensitivity: (True positive/[True positive + False negative]) $25/[25 + 2] = 93\%$. Of all the people *with the disease*, the number that will have a *positive test*.
Specificity: (True negative/[True negative + False positive]) $100/[100 + 1] = 99\%$ Of all the people *without the disease*, the number that will have a *negative test*
2. Positive predictive value: (True positive/[True positive + False positive]) $200/[200 + 10] = 95\%$.

Of all the people with a *positive test*, the number that *will* have the *disease*.

Negative predictive value: $(\text{True negative} / [\text{True negative} + \text{False negative}]) = 770 / [770 + 20] = 97\%$.

Of all the people with a *negative test*, the number that *will not* have the *disease*.

3. B. A normal distribution is a bell shaped curve (1 peak) where approximately 68% of the results fall within 1 standard deviation and about 95% within 2 standard deviations. Since the mean is the average number and the median is the value that half the population falls below, these numbers can be very close when values follow a normal distribution.
4. C. One major objective of trials is to have the results apply to those outside of the study population. When a trial has low external validity, the therapy is found to be best for the population studied only. Internal validity takes into account whether the trial was done properly and had valid findings.
5. $\text{NNT} = 1 / [(\text{Rate in untreated group}) - (\text{Rate in treated group})] = 1 / (18\% - 5\%) = 1 / 0.13 = 8$
6. Your decision that a treatment is not different when it really is not different, is a correct answer. Similarly, concluding that the treatments are different when in reality they are different is also a true statement. A type I error is committed when there is no difference between treatments but on the basis of the study the investigators erroneously conclude that they are different. The probability of making this error is the P value (or alpha). A type II error occurs when there really is a difference between therapies but on the basis of the study, it is erroneously concluded that there is no difference. The probability of making this error is β . Since the total of all probabilities are equal to 1, the probability that the investigators correctly decide on the basis of their study that the treatments are correctly different is $1 - \beta$ (or power).
7. C. The power of a study tells the investigator how good the study is at correctly identifying a difference between the treatments being tested, if in reality they actually are different. In other words, how likely is the study NOT to miss a difference if one really exists? Thus all are true statements except for C. The probability of making a type I error is the P value (or alpha).
8. D. A cohort design involves a study population that is followed for a long period of time to determine whether an outcome of interest has occurred i.e., it begins with exposed and non exposed subjects.

In a concurrent cohort study (also known as prospective or longitudinal) the study follows the subjects through time until the point at which the outcome develops or not. This is problematic when studying something that takes a long time to develop. Using data from 1980, the observation time will be shortened. For this reason it is called a retrospective cohort (or a historical cohort or nonconcurrent prospective study). In the end, exposed and nonexposed groups will be compared. In a cross sectional study both exposure and disease outcome are determined at the same time for each subject. It looks only at one point in time. Case control studies start with those who have the disease outcome and compares them to those without. Randomized controlled trials involve 2 groups that are randomized to an intervention and followed for the outcome.

$$9. \text{OR} = ([A \times D] / [B \times C]) \\ (10 \times 1000) / (200 \times 60) = 0.83$$

10. B. The U.S. Food and Drug Administration follows a standard protocol in testing new pharmaceutical agents. Phase 1 are small studies that evaluate the agent for toxic and pharmaceutical effects while phase 2 are larger that look for efficacy and safety. phase 3 are large randomized controlled trials that test for effectiveness and safety, which if successful would then be approved for marketing. phase 4 studies are postmarketing surveillance that will continue the study for safety and effectiveness as it is used by the public.

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HISTOLOGIC STAINS AND SPECIAL STUDIES

HAFEEZ DIWAN
VICTOR G. PRIETO

HEMATOXYLIN AND EOSIN (H&E)

- Used for elucidation of basic histologic features, prior to the use of special stains or immunohistochemical studies as needed; among other features, calcification and microorganisms such as fungi and bacteria may be detected by H&E and confirmed by additional studies

STAINS FOR CARBOHYDRATES

- Periodic-acid Schiff (PAS)
 - Stains glycogen red—diastase labile; therefore, diastase pretreatment will remove glycogen
 - Stains mucopolysaccharides red—diastase stable
 - Stains fungi red—diastase stable
 - Stains basement membrane red—diastase stable
- Colloidal iron
 - Stains mucin blue
- Alcian blue
 - Stains mucopolysaccharides blue
 - At pH 2.5: acid (carboxylated or sulfated mucopolysaccharides)
 - At pH 1.0: acid (sulfated mucopolysaccharides)
 - With hyaluronidase: only epithelial mucins will stain (connective tissue mucins will be digested and will not stain)
 - With PAS: acid mucopolysaccharides will stain blue and neutral polysaccharides will stain magenta; also, the yeast of *Cryptococcus* will stain red and the capsule will stain blue with this method
- Mucicarmine
 - Stains epithelial mucins red (also stains capsule of *Cryptococcus* red)

STAINS FOR PIGMENTS

- Fontana-Masson (Fig. 30-1)
 - Stains melanin and argentaffin granules black (nuclei will be red); useful for quantifying melanocytes (e.g. in vitiligo) and in cases of minocycline pigmentary alteration
 - Also stains *Cryptococcus*
- Grimelius argyrophil stain
 - Argentaffin and argyrophil substances will stain black
- Tyrosinase (DOPA-oxidase)
 - Requires fresh tissue
 - Stains melanin-containing cells brownish-black (due to tyrosinase acting on DOPA, the substrate for this reaction)

STAINS FOR MINERALS

- Von-Kossa
 - Stains calcium salts black; useful for detecting calcification of vessel walls and elastic tissue (calcinosis cutis, pseudoxanthoma elasticum, calciphylaxis, elastosis and elastofibroma)
- Alizarin red S
 - Stains calcium red
- Prussian blue stain (Fig. 30-2)
 - Stains iron blue (the Prussian blue reaction: tissue treated with dilute hydrochloric acid and potassium ferrocyanide)
- Gomori methenamine silver (GMS) (Fig. 30-3)
 - Stains urates black. {Note: urates are lost if tissue is processed in formalin}

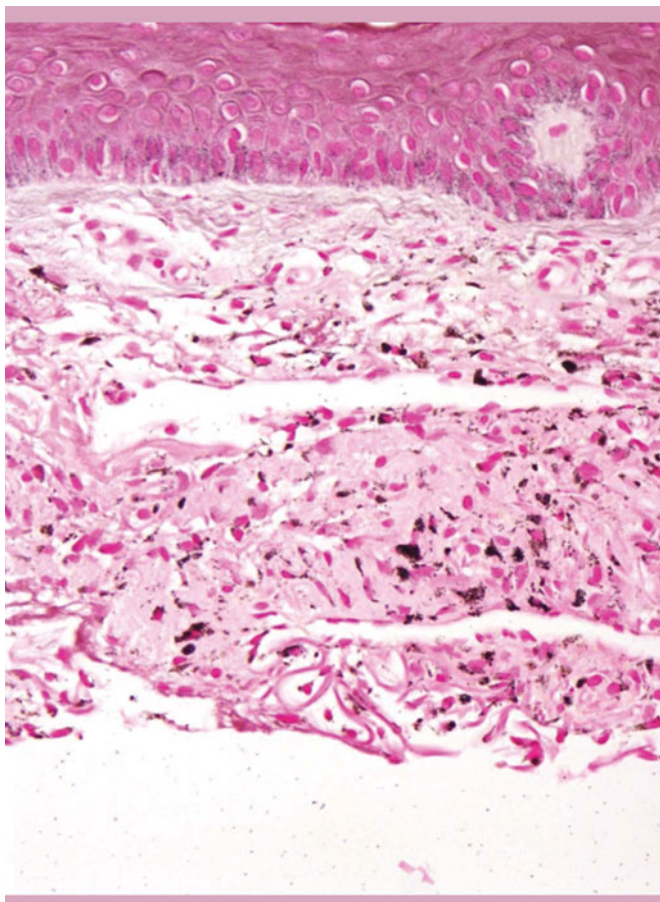


FIGURE 30-1 Fontana-Masson stains melanin black in this biopsy of minocycline pigmentation (200x) (also see Fig. 30-3).

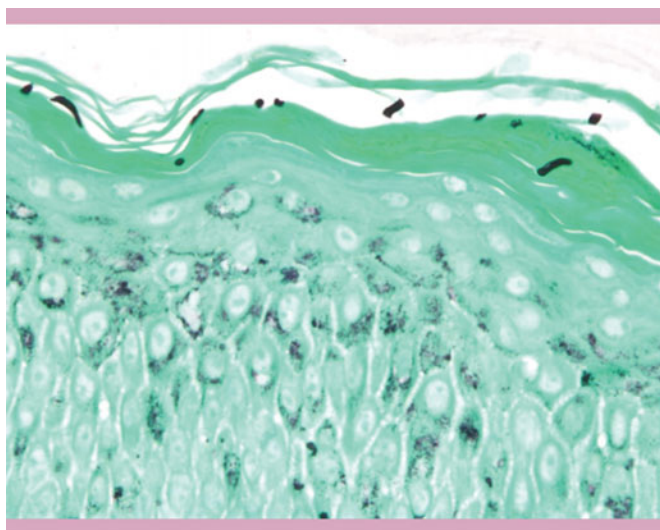


FIGURE 30-2 GMS stain showing dermatophytes in stratum corneum (200x).

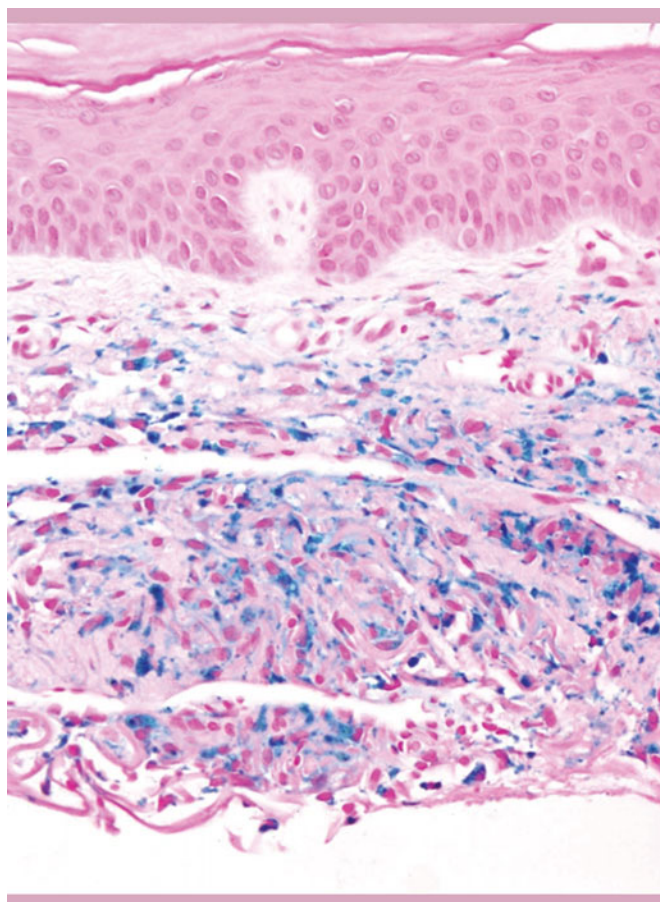


FIGURE 30-3 Prussian blue stains iron blue (200x). This is a case of minocycline pigmentation, which was also Fontana-Masson positive.

- Tissue must be processed with alcohol to prevent loss of urates
- Also see Stains for Microorganisms below

STAINS FOR CONNECTIVE TISSUE COMPONENTS

- Trichrome
 - Stains collagen blue or green and muscle red, depending on the type of reagents used
- Verhoeff-van Gieson
 - Stains elastic fibers black, collagen red, and muscle yellow (also red cells will stain yellow)

STAINS FOR AMYLOID

- Congo red
 - Stains amyloid pinkish-red; gives apple-green birefringence to amyloid (the most specific method for amyloid)

- Thioflavin T
 - Amyloid shows yellow fluorescence
- Crystal violet
 - Stains amyloid purple-violet

STAINS FOR FAT

- Oil red O
 - Stains fat red; needs frozen/fresh tissue (once tissue is fixed and processed into paraffin blocks, this method does not work). This may be very helpful in seeing the fat globules in sebaceous carcinoma.
- Osmium tetroxide
 - Paraffin-embedded tissue; stains fat black
- Sudan black B
 - Paraffin-embedded tissue; stains fat black

STAINS FOR MICROORGANISMS

- H&E
 - May demonstrate fungi, bacteria
- Gram
 - Stains gram-positive bacteria (also *Nocardia*) dark blue and gram-negative organisms red
- Giemsa
 - For *Leishmania* and granuloma inguinale
- Gomori methenamine silver (GMS) (Fig. 30-3)
 - Stains fungi, *Pneumocystis jiroveci* (formerly *carinii*), and protothecosis black
- PAS
 - Stains fungi and protothecosis pink
- Fontana-Masson (Fig. 30-1)
 - Stains *Cryptococcus*
- Warthin-Starry
 - Stains spirochetes black
- Ziehl-Neelson stain
 - Uses carbol fuchsin; stains mycobacteria red
- Fite stain (Fig. 30-4)
 - Modification of Ziehl-Neelson; stains *Mycobacterium leprae* and *Nocardia*
 - It also detects atypical mycobacteria

STAINS FOR MAST CELLS

- Giemsa and toluidine blue are metachromatic stains for mast cells; also chloroacetate esterase (Leder stain)

IMMUNOHISTOCHEMICAL STUDIES

- Uses primary antibodies (polyclonal or monoclonal) to a particular antigen, followed by secondary

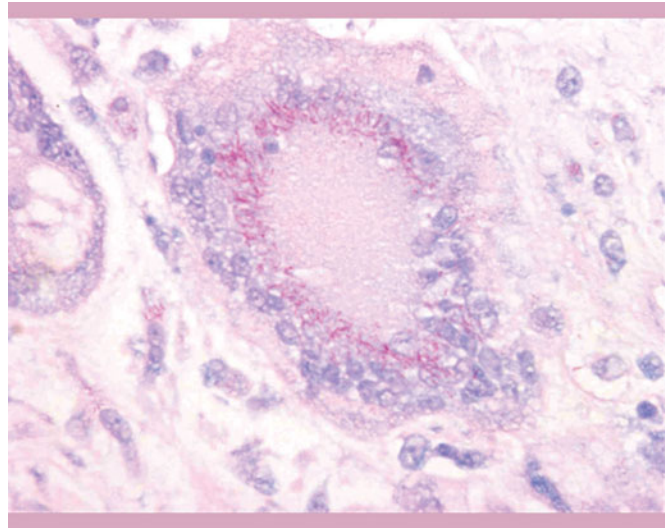


FIGURE 30-4 Fite stain showing atypical mycobacteria pink inside giant cells (400x). This case was thought to be erythema nodosum clinically.

antibody complexed to an enzyme; subsequently, a chromagen is added, which is acted on by the enzyme, releasing a colored product that is evaluated histologically

STUDIES FOR EPITHELIA

- Cytokeratins (CK) are intermediate filaments found in epithelial cells; the following antibodies and cocktail antibodies are useful (Figs. 30-5 and 30-6)
- AE1/AE3—a cocktail antibody recognizing a broad spectrum of keratin; it labels most squamous cell carcinomas (SCC), basal cell carcinomas (BCC), adnexal tumors, and Merkel cell carcinomas but it may not label spindle cell SCC
- CAM5.2—useful for eccrine tumors, Paget's disease (PD), extramammary Paget's disease (EMPD), and will also label sebaceous carcinoma and a minority of BCC; SCC is mostly negative, however
- CK5/6—useful for SCC, including spindle cell SCC; it has been shown to label the majority of primary cutaneous adnexal neoplasms and may be useful in distinguishing these from metastatic adenocarcinoma to the skin (fewer of these are reactive with anti-CK5/6) (see also p63)
- CK7—Very useful for demonstrating PD and EMPD; present in less than a quarter cases of Merkel cell carcinoma
- CK20—Merkel cell carcinoma will typically exhibit perinuclear dot-like positivity

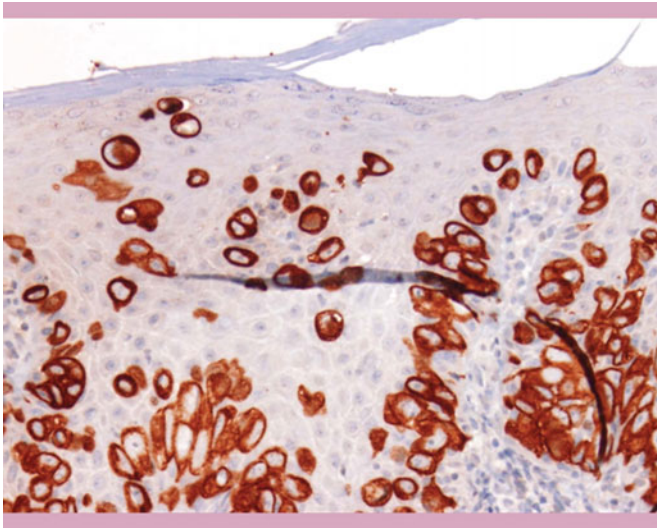


FIGURE 30-5 Cytokeratin 7 immunopositivity in extramammary Paget's disease in the perianal region (200x).

- CEA (carcinoembryonic antigen)
 - Antibody to CEA, which is an oncofetal antigen, will demonstrate glandular differentiation (helpful in eccrine and apocrine adnexal neoplasms)
 - It will also be positive in the ducts of sebaceous carcinoma
 - It is extremely useful to demonstrate EMPD but may not be as good for PD
- EMA (epithelial membrane antigen)
 - Positive in numerous tumors: EMPD, PD, adnexal neoplasms especially sebaceous neoplasms, perineuromas, and focally positive in most SCC and in epithelioid sarcoma; also positive in plasma cells and some CD30 anaplastic large cell lymphomas
- GCDFP (gross cystic disease fluid protein)
 - Positive in PD, EMPD, and adnexal neoplasms; breast carcinomas are also labeled

STUDIES FOR MESENCHYMAL TISSUE

- Actin antibodies (smooth muscle actin)
 - Useful in demonstrating leiomyoma/leiomyosarcoma, glomus tumors, and dermatomyofibroma
 - Cellular neurothekeoma will also exhibit positivity in 50% of cases
- Desmin
 - For leiomyoma/leiomyosarcoma, angiomyofibroblastoma
- CD34
 - Very useful for dermatofibrosarcoma protuberans (DFSP); it is positive in vascular tumors such as

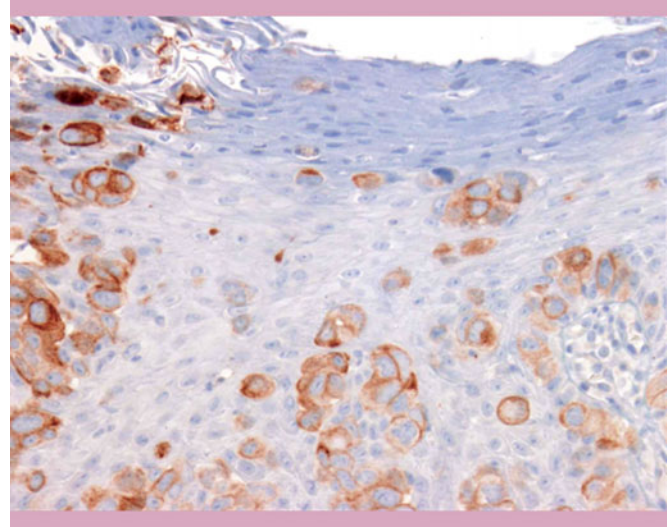


FIGURE 30-6 Cytokeratin 20 immunopositivity in perianal extramammary Paget's disease (200x). CK20 may be positive in EMPD with underlying gastrointestinal malignancy.

- hemangioma, angiosarcoma, Kaposi's sarcoma, and lymphangioma and is also positive in nearly half the cases of epithelioid sarcoma
- CD31
 - It is positive in vascular neoplasms: angiosarcoma, hemangioma, lymphangioma, Kaposi's sarcoma; also positive in macrophages (which is a possible pitfall)

STUDIES FOR NEUROECTODERMAL LESIONS

- S-100
 - Not very specific but extremely sensitive for primary melanoma (including desmoplastic melanoma), metastatic melanoma, and nevi; also positive in a variety of other tumors such as breast carcinoma, Rosai-Dorfman disease, granular cell tumor, neurofibroma, schwannoma, myxoid neurothekeoma, chondroid syringoma, syringoma, and Langherhans cell histiocytosis
- S-100A6 is positive in cellular neurothekeomas and some melanocytic lesions
- MART-1 (melanoma antigen recognized by T-cells) – Two main antibodies (M2 and A103)
 - Less sensitive and more specific than S-100 for melanocytic lesions; only a minority of cells in a proportion of desmoplastic melanoma label with this marker
- It is also positive in adrenocortical carcinoma and angiomyolipoma (among others), particularly the clone A103

- HMB45 and Ki-67
 - HMB45 is less sensitive and more specific than S-100 for melanocytic lesions; it reacts with gp100, a glycoprotein present in premelanosomes
 - Only a minority of cells in a proportion of desmoplastic melanoma label with this marker
 - This is a useful marker to demonstrate maturation in melanocytic lesions: i.e., melanocytic cells in the dermis label at the top of benign melanocytic lesions but not at the bottom; in suspicious lesions, demonstration of maturation may be helpful in arguing against a diagnosis of melanoma
 - Ki-67 is an antigen present in all cells not in G₀ (resting) phase. The most common antibody is Mib-1.
 - Regarding blue nevi versus spindle cell melanoma, the former are strongly, diffusely positive with HMB45; HMB45 is especially useful in this context when used together with Ki-67, a marker of proliferation
 - Melanocytic cells in the dermis that show maturation with HMB45 and show low proliferation (less than approximately 5% of cells reacting with Ki-67) are less likely to be melanoma; of course, it is not possible to be absolutely certain about this, but in the appropriate clinical context, it may provide helpful information
- CK20 (see above)
- Synaptophysin and chromogranin
 - Both of these markers may be positive in Merkel cell carcinoma
- CD57
 - Labels a small proportion of cellular neurothekeoma and neurofibroma
- PGP9.5
 - It is positive in cellular neurothekeoma; it is not very specific, though, and is positive in many other tumors, including Merkel cell carcinoma and dermatofibroma
- NKI/C3
 - It is a macrophage marker positive in cellular neurothekeoma, but is not very specific
- Marks T cells (T-helper cells), Langerhans cells, and macrophages; in mycosis fungoides, typically CD4 predominates over CD8
- CD5
 - Marks T cells; it is also positive in B cells in chronic lymphocytic leukemia (CLL) and mantle zone lymphoma. CLL lymphocytes would be expected to be CD5 and CD20 positive.
- CD7
 - Marks T cells
 - It may be useful in MF in the following manner: it may not be present on epidermal lymphocytes that mark with CD4 and CD3, for example, suggesting loss of expression; however, inflammatory lesions may also exhibit this feature
- CD8
 - Marks T cells (T-cytotoxic/suppressor cells) (see CD4 above)
- CD20 (Figs. 30-7 and 30-8)
 - Marks B cells; may be useful, along with CD3, kappa and lambda in showing that a

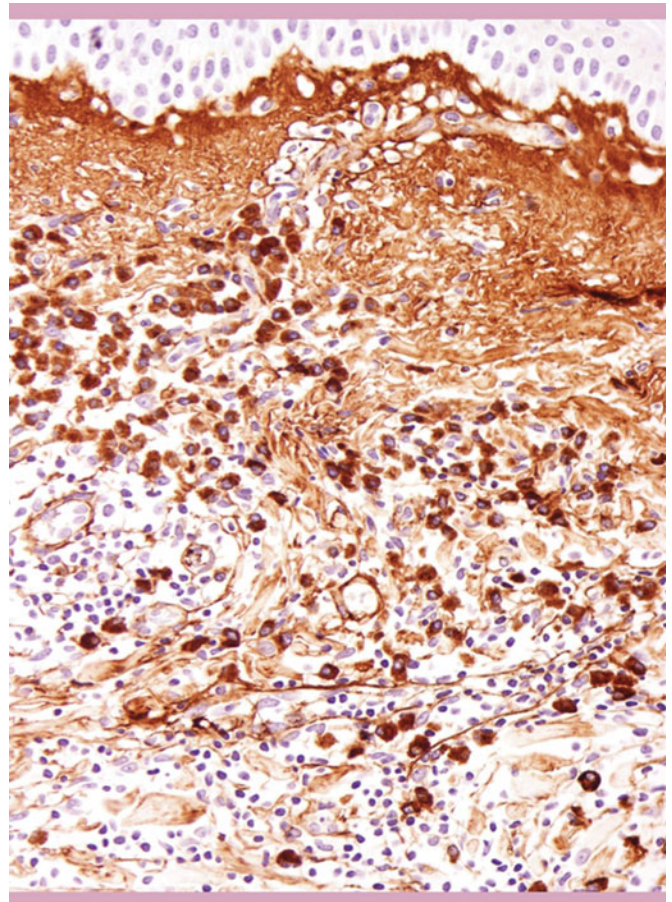


FIGURE 30-7 Kappa immunoreactivity in cutaneous Marginal zone lymphoma (200x). The majority of the plasma cells were kappa positive and lambda negative.

STUDIES FOR HEMATOPOEITIC LESIONS

- CD1a
 - Marker for Langerhans cells (and therefore useful in Langerhans cell histiocytosis)
- CD3
 - Marks T cells
- CD4

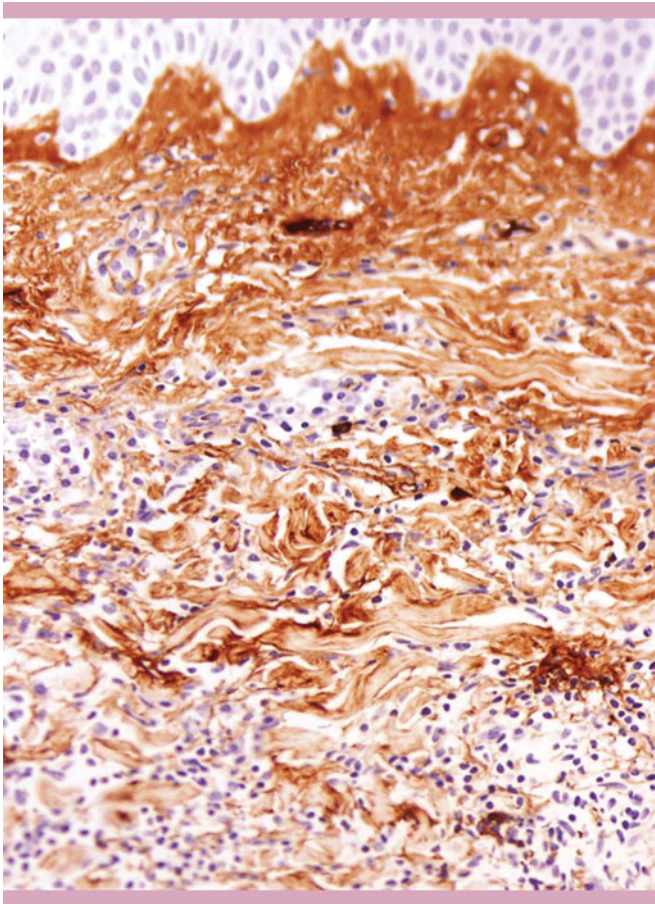


FIGURE 30-8 Lambda positive immunoreactivity. Only rare plasma cells are lambda positive in this case of Marginal zone lymphoma (200x).

lymphoid infiltrate in the skin is composed of heterogeneous cells, and therefore likely to be reactive rather than neoplastic (not always true, however)

- CD21
 - Marks B cells and follicular dendritic cells; positive in follicular dendritic cell sarcoma
- CD30
 - Marks activated T cells (among others)
 - It labels the majority of cells in anaplastic T-cell lymphoma (ALCL) (primary cutaneous ALCL shows less positivity for ALK-1 as compared to systemic ALCL; nevertheless, ALK-1 may be positive in a minority of primary cutaneous ALCL)
 - CD30 also labels large cells in lymphomatoid papulosis (types A and C; also, to a lesser extent, type B)
 - It is very rarely found in cutaneous B-cell lymphoma
- CD34
 - Helpful marker for leukemia cutis

- CD35
 - Marks follicular dendritic cells; positive in follicular dendritic cell sarcoma
- CD45
 - Marks most hematopoietic cells (ALCL may be negative)
- CD56 (neuronal cell adhesion marker-NCAM)
 - Marker for NK cell lymphoma
 - Leukemic cells may be positive as well; also positive in neural neoplasms such as neurofibroma myxoid neurothekeoma and in desmoplastic melanoma
- CD57 (see above)
- Mast cell tryptase
 - Positive in mast cells
- MPO (myeloperoxidase)
 - Antibody to MPO may label leukemic cells; also labels neutrophils and monocytes (note that there is a histochemical stain for MPO as well, with similar usefulness)
- Kappa and lambda
 - Presence of light-chain restriction, i.e., a plasmacytic infiltrate that is either kappa or lambda positive is seen in conditions such as myeloma and marginal zone lymphoma. Normally, a mixture of both with a kappa predominance is expected.

STUDIES FOR INFECTIOUS DISEASES

- The following is a list of useful antibodies:
 - HHV-8: kaposi's sarcoma
 - Spirochetal antibody: syphilis
 - Herpes-simplex antibody: for demonstrating *Herpes simplex* virus
 - Herpes-zoster antibody: for demonstrating zoster

QUIZ

Questions

1. Biopsy of a lesion on the scrotum of a 65-year-old male shows pagetoid cells in the epidermis. Which of the following combinations of studies may be helpful in diagnosing this case?
 - A. CK20, S-100, Mart-1, CK7 and CEA
 - B. CD1a, CD5, S-100, PAS and GMS
 - C. CK20, CD1a, PAS, GMS and CD1a
 - D. EMA, CD1a, CD5, CD3 and GMS
2. A biopsy shows small lymphocytes in dense aggregates in the subcutaneous tissue. Immunohistochemical studies reveal that these are CD5 and CD20 positive. The best diagnosis is:

- A. Acute myeloid leukemia
 - B. Chronic myeloid leukemia
 - C. Acute lymphocytic leukemia
 - D. Chronic lymphocytic leukemia
3. Which of the following may be helpful in evaluating mast cells?
 - A. Anti-trypsin antibody
 - B. Anti-tryptase antibody
 - C. GMS
 - D. Gram
 4. In a case of suspected Merkel cell carcinoma, which of the following studies may be negative?
 - A. CK20
 - B. Cytokeratin
 - C. CEA
 - D. CD56
 5. An immunocompromised patient presents with pulmonary lesions and a widespread papular eruption. Biopsy of a skin lesion reveals probable fungal organisms that are GMS and Fontana-Masson positive. The most likely diagnosis is:
 - A. Coccidioidomycosis
 - B. Cryptococcosis
 - C. Histoplasmosis
 - D. Systemic candidiasis
 6. A biopsy of a papule on the arm shows lymphoid aggregates with apparent germinal centers with a cuff of plasma cells around them. Immunohistochemical studies show the following: CD3 – positive; CD20 – positive; kappa – negative; lambda – numerous positive plasma cells. The best diagnosis is:
 - A. Secondary syphilis
 - B. Mantle cell lymphoma
 - C. Marginal zone lymphoma
 - D. Lupus
 7. A 2-year-old boy has crusted, ulcerated lesions on the scalp and forehead. The dermatopathologist informs you that an immunohistochemical study shows numerous CD1a positive cells in the epidermis. Which other immunohistochemical study may be positive in this case?
 - A. S-100
 - B. Mart-1
 - C. CK7
 - D. CD5
 8. A 14-year-old Caucasian male has hypopigmented patches on the elbows. You suspect vitiligo and perform a biopsy. Which of the following studies may be useful in this case?
 - A. Fontana-Masson
 - B. PAS
 - C. Giemsa
 - D. Prussian blue
 9. One of your colleagues, a Mohs surgeon, removes a lower eyelid lesion. He shows you the frozen section and you see somewhat clear cells in the epidermis. Which of the following studies may be useful in evaluating the frozen section slide and arriving at a diagnosis?
 - A. Giemsa
 - B. Oil red O
 - C. GMS
 - D. Leder stain
 10. A 23-year-old HIV-positive male presents with reddish lesions on his leg. The dermatologist performs a biopsy and writes a note to the dermatopathologist. Which of the following is the most likely note written by the dermatologist?
 - A. "Please perform a Warthin-Starry stain"
 - B. "Please perform a Leder stain"
 - C. "Please perform an HHV-8 immuno study"
 - D. "Please perform a CMV immuno study"

Answers

1. A. In EMPD, CK7 and CEA should be positive. CK20 positivity is seen less frequently, but may be seen associated with underlying gastrointestinal malignancy. Of course, in a pagetoid lesion, it is important to rule out melanoma in situ, and S-100 and Mart-1 will be expected to be negative.
2. B. Chronic lymphocytic leukemia/small lymphocytic lymphoma tumor cells have both CD5 and CD20 positivity.
3. C. Antibody to mast cell tryptase can highlight the mast cells. Mast cells may be evaluated with Giemsa and Leder stains as well.
4. D. Merkel cell carcinoma shows characteristic dot-like CK20 positivity, cytokeratin positivity and also CD56. CEA is not typically positive.
5. E. Cryptococcus, like other fungi, is GMS and PAS positive. Interestingly, it is also Fontana-Masson positive.
6. C. Marginal zone lymphoma can look deceptively like cutaneous lymphoid hyperplasia because of the presence of reactive appearing lymphoid aggregates and germinal centers. A clue to the diagnosis on H&E is the presence of plasma cells around the

aggregates of lymphocytes. Therefore, kappa and lambda immunohistochemical studies to show light chain restriction can be very helpful in arriving at the correct diagnosis.

7. A. The presentation is that of Langerhans cell histiocytosis. The tumor cells are CD1a and S-100 positive. This is an important thing to remember since S-100 positive intraepidermal cells are not always melanocytic cells—they may be Langerhans cells.
8. A. The absence of any melanin (which would be detected by Fontana-Masson) would be expected in vitiligo.
9. B. In cases of sebaceous carcinoma, a fat stain (such as an Oil red-O stain that gives fat a red-orange color) is very useful. It generally works in the frozen section setting, since the process of fixation leads to loss of fat.
10. C. Since the most likely diagnosis is Kaposi's sarcoma, an HHV-8 would be expected to be positive in the lesion.

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DERMOSCOPY

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SYNONYMS

- Dermatoscopy
- Skin surface microscopy
- Epiluminescence microscopy (ELM)
- Digital dermoscopy/digital ELM
- Auflichtmikroskopie (German)
- Dermoscopia/dermatoscopia (Spanish)
- Dermoscopy is the term used by experienced dermoscopists and is most commonly used in the literature

DEFINITION

- Dermoscopy is an in-vivo, non-invasive technique in which oil or fluid (e.g., mineral oil, gels, alcohol and water) is placed on the lesion
 - Fluid eliminates reflection of light from the surface of the skin allowing visualization of color and structure in the epidermis, dermo-epidermal junction and papillary dermis
 - The color and structure visualized cannot be seen with the naked eye or with typical magnification that clinicians use
 - Polarizing light and digital instrumentation do not require fluid
- When using polarized light dermoscopy
 - Light from a polarized light source penetrates the stratum corneum with less scatter
 - A second polarizer screens out scattered surface light resulting in the physician seeing primarily light from the deeper structures
 - This removes the need for contact with the skin and the need for immersion fluids, resulting in faster examination times

BENEFITS OF DERMOSCOPY

- Helps to differentiate melanocytic from non-melanocytic skin lesions

- Helps to differentiate benign from malignant skin lesions
- With dermoscopy the diagnostician's sensitivity to diagnose melanoma is 85% and better compared to 65–80% when the technique is not used
- Increases the diagnosis of early melanoma
- Increases the diagnosis of melanoma in situ (false negative melanoma)
- Helps to avoid unnecessary surgery
- Helps to plan surgery
- Helps to work better with a pathologist (asymmetrical high risk criteria, dermoscopic – pathologic correlation)
- Patient reassurance
- Allows for follow up of patients with multiple nevi digitally to find changes over time

DERMOSCOPIC DIGITAL MONITORING

- There are pigmented skin lesions that are not high risk enough to warrant immediate histopathologic diagnosis, yet not so banal that there is no concern at all
- There are melanomas that do not appear to be high risk clinically or with dermoscopy
- They are only diagnosed after monitoring for dermoscopic changes over time when comparing baseline with subsequent digital images
- Short-term monitoring is performed every three or four months
 - Any change over time could be a melanoma
- Long term monitoring is done at 6-month to yearly intervals
 - Important changes include asymmetrical enlargement, the appearance of high risk criteria, new colors, or regression
- Single or multiple suspicious pigmented skin lesions can be chosen for digital monitoring

THE TWO STEP ALGORITHM

- The analysis of a suspicious skin lesion is a two-step process
 - Step one: determine if it is melanocytic or non-melanocytic
 - Step two: if it has the criteria for a melanocytic lesion, the second step is to determine if it is low, intermediate or high risk using the melanocytic algorithm of your choice
- Pattern analysis was the first melanocytic algorithm developed for this purpose and is most often used by experienced dermoscopists. Variations of pattern analysis (the simplified algorithms) have also been developed, including:
 - The ABCD rule of dermatoscopy (the second algorithm developed) (Table 31-1)
 - The Seven Point Checklist (Table 31-2)
 - Menzies Method (eleven point checklist) (Table 31-3)
 - The newest three-point checklist (Table 31-4)

Step One: Identification of Criteria

Look for the criteria associated with a melanocytic lesion (Table 31-5). If one does not find them, the search is on for the criteria associated with seborrheic keratosis, basal cell carcinoma, dermatofibromas, vascular lesions and others

- Not all of the possible criteria are needed to make a diagnosis
- When there is absence of criteria for a melanocytic lesion, seborrheic keratosis, basal cell carcinoma, dermatofibroma or vascular lesion, you are now dealing with a melanocytic lesion by default
- The “default category” is the last criterion used to diagnose a melanocytic lesion (Fig. 31-1)

CRITERIA DEFINED

- Melanocytic Lesion
 - *Pigment network/network/reticulation*
 - On the trunk and extremities
 - Black, brown or gray
 - Honeycomb-like, reticular, web-like line segments (elongated and hyperpigmented rete ridges) with hypopigmented holes (dermal papilla)
 - *Pseudonetwork/ Pseudopigment network*
 - Because the skin of the head and neck is thin and does not have well developed rete ridges, one sees
 - ▲ Appendageal openings/adnexal structures (sebaceous glands, hair follicles)
 - ▲ Uniform, round white or yellowish structures
 - When they penetrate areas of diffuse pigmentation, reticular like structures are formed that is referred to as the pseudonetwork
 - Monomorphous appendageal openings can often be seen on the skin of the face without any pigmentation
 - They should not be confused with the milia-like cysts seen in seborrheic keratosis
 - It is not always possible to make the differentiation
 - Consequences could be misdiagnosing lentigo-maligna for a seborrheic keratosis
 - This criterion can also be seen with non-melanocytic lesions
 - In the strictest sense of the definition it is not 100% diagnostic of a melanocytic lesion
 - *Dots and Globules*
 - Roundish structures distinguished only by their relative sizes

TABLE 31-1 ABCD Rule of Dermatoscopy: Identify Criteria and assign Points to Determine Total Dermatoscopy Score (TDS)

Dermoscopic Criterion	Definition	Score	Weight Factor
Asymmetry:	In 0, 1, or 2 perpendicular axes; assess contour, colors and structures	0-2	
Border:	Abrupt ending of pigment pattern at periphery in 0-8 segments	0-8	
Color:	Presence of up to 6 colors (white, red, light-brown dark-brown blue-gray, black)	1-6	
Dermoscopic structures:	Presence of network, structureless (homogeneous) areas, branched streaks, dots, and globules	1-5	
Formula for calculating total dermatoscopy score (TDS): (A score x 1. 3) + (B score x 0.1) + (C score x 0. 5) + (D score x 0. 5) = TDS. Interpretation of total score: <4.75. Benign melanocytic lesion			
4.75-5.45; suspect lesion (close follow-up or excision recommended); > 5.45, lesion highly suspect for melanoma.			

TABLE 31-2 Menzies Scoring Method: 11 Point Check List

Dermoscopic Criterion
1. Negative features
2. Symmetry of pattern
3. Presence of single color
4. Positive features
5. Blue-white veil
6. Multiple brown dots
7. Pseudopods (streaks)
8. Radial streaming (streaks)
9. Scar-like depigmentation
10. Peripheral black dots/globules
11. Multiple (5 or 6) colors
12. Multiple blue/gray dots
13. Broadened network

For melanoma to be diagnosed, both negative features must be absent and one or more of the 9 positive features must be present.

TABLE 31-3 7-Point Checklist

Dermoscopic Criterion	Scores
1. Atypical pigment network (major criteria)	2
2. Blue-whitish veil	2
3. Atypical vascular pattern	2
4. Irregular streaks (minor criteria)	1
5. Irregular dots/globules	1
6. Irregular blotches	1
7. Regression structure	1

By simple addition of the individual scores a minimum total score of 3 is required for the diagnosis of melanoma, whereas a total score of less than 3 is indicated of non melanoma.

TABLE 31-4 Three Point Checklist to Diagnose High-Risk Lesions (Melanoma, Basal Cells)

1. Asymmetry of color and or structure
2. Irregular pigment network
3. Blue and / or white color
2 out 3, 3 out 3 → Excise

The three point check list is based on simplified pattern analysis and is intended to be used by non-expert dermoscopists as a screening technique. It's aim is to diagnose melanocytic and non-melanocytic potentially malignant pathology.

- Dots (0.1 mm) are smaller than globules (greater than 0.1 mm)
 - Black, brown, gray or red
 - ▲ When black, they can represent atypical melanocytes in the epidermis
 - ▲ Regular brown dots and globules represent nests of melanocytes at the dermo-epidermal junction
 - ▲ Irregular brown dots and globules represent nests of atypical melanocytes at the dermo-epidermal junction
 - ▲ Grayish dots (“peppering”) represent free melanin and melanophages in the papillary dermis, which can be seen in regression areas or alone in benign pathology such as late stage lichen planus-like keratosis or post traumatic
 - ▲ Reddish globules can be seen in melanoma (neovascularization)
- It is written and taught that aggregated globules identify a melanocytic lesion with no mention of the smaller dots. The reality is that both dots and globules define a melanocytic lesion (Fig. 31-2)
 - Homogeneous blue pigmentation
 - Structureless blue color in the absence of local criteria such as pigment network, dots or globules (Fig. 31-3)
 - Many variations of homogeneous blue color usually represents a blue nevus
 - The history is important because there is a differential diagnosis which could include
 - ▲ A lesion as banal as a radiation tattoo to one more ominous such as nodular or cutaneous metastatic melanoma
 - Parallel patterns/ acral patterns
 - Fissures and ridges on the skin of the palms and soles (dermoglyphics)
 - Can create parallel patterns

Table 31-5 Criteria for Various Lesions

Criteria for a melanocytic lesion:	Pigment network (trunk and extremities) Pseudopigment network/pseudo network (head and neck) Aggregated globules Homogeneous blue color of a blue nevus Parallel patterns on acral sites By default
Criteria for a seborrheic keratosis:	Milia-like cysts Follicular openings Fissures and ridges Fingerprint pattern Hairpin shaped vessels Moth-eaten borders Sharp demarcation
Criteria for a basal cell carcinoma:	Absence of criteria for a melanocytic lesion Arborizing blood vessels Pigmentation Ulceration Spoke-wheel structures
Criteria for a dermatofibroma:	Central white patch Peripheral pigment network
Criteria for a vascular lesion:	Vascular spaces called lacunae

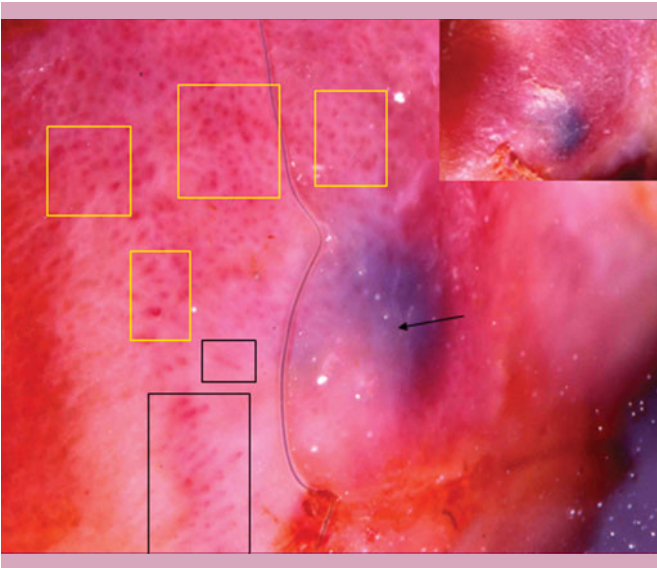


FIGURE 31-1 Amelanotic melanoma. This is a melanocytic lesion by default because there is an absence of criteria for a melanocytic lesion, seborrheic keratosis, basal cell carcinoma, dermatofibroma or hemangioma. The blue-white color (arrow) is a clue that this might be a melanocytic lesion. There are pinpoint/dotted (yellow boxes) and irregular linear (black boxes) vessels plus a general milky-red background color. Note: This interdigital melanoma was mistakenly treated as a tinea for two years.

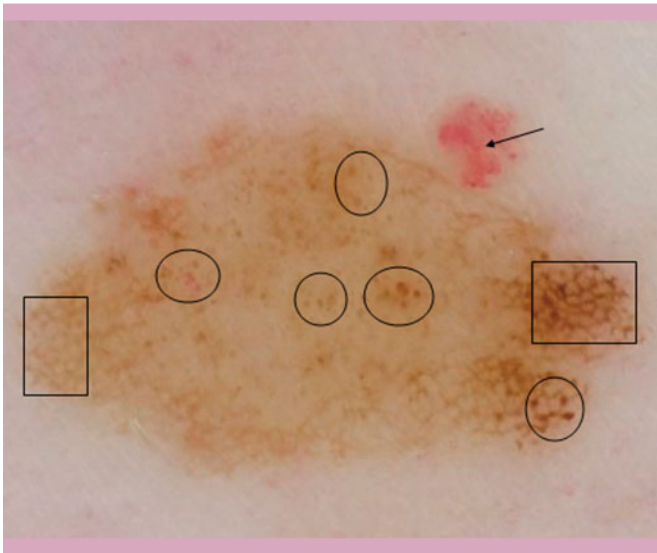


FIGURE 31-2 Acquired nevus. This is a melanocytic lesion because it has pigment network (black boxes) and aggregated globules (circles). There is a small hemangioma adjacent to the nevus (arrow).

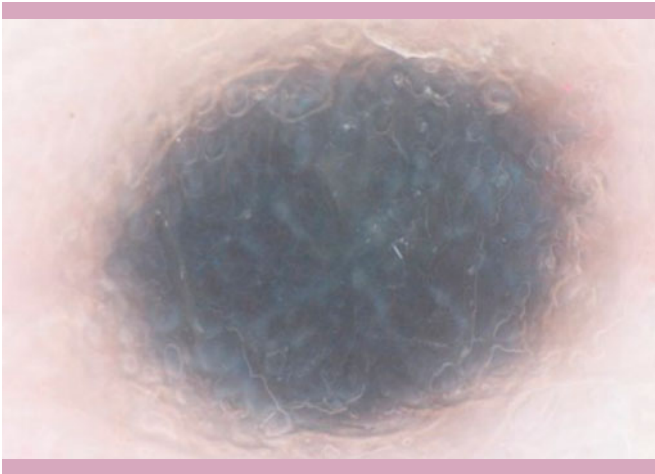


FIGURE 31-3 Blue nevus. The classic homogenous blue color of a blue nevus.

- *Parallel-furrow pattern (benign pattern)*
 - Thin brown parallel lines in the furrows of the skin (crista superficialis limitans)
 - Variations include two thin lines with or without dots and globules (Fig. 31-4)
- *Lattice-like pattern (benign pattern)*
 - Thin brown parallel lines in the furrows
 - Running perpendicular to the furrows forming a ladder-like picture (Fig. 31-5)
- *Fibrillar pattern (benign pattern)*
 - Fine brown lines
 - Run in an oblique (/////) direction
 - Pressure can change the lattice-like pattern into a fibrillar pattern
- *Globular pattern (benign)*
 - Brown globules without a parallel component

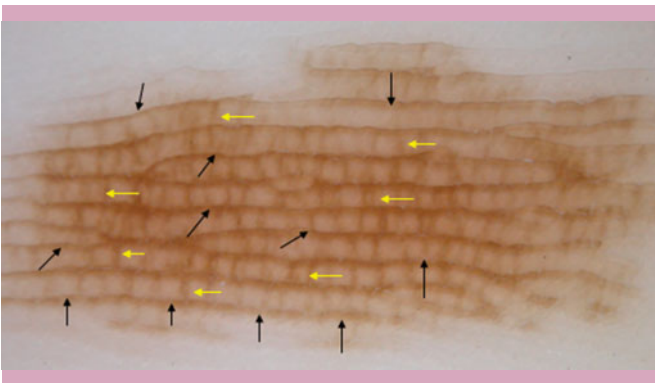


FIGURE 31-5 Acral nevus. Brown lines in the furrows (black arrows) and perpendicular to the furrows (yellow arrows) characterize the lattice-like pattern. Pressure on the foot can change this into the fibrillar pattern with fine oblique (/////) lines.

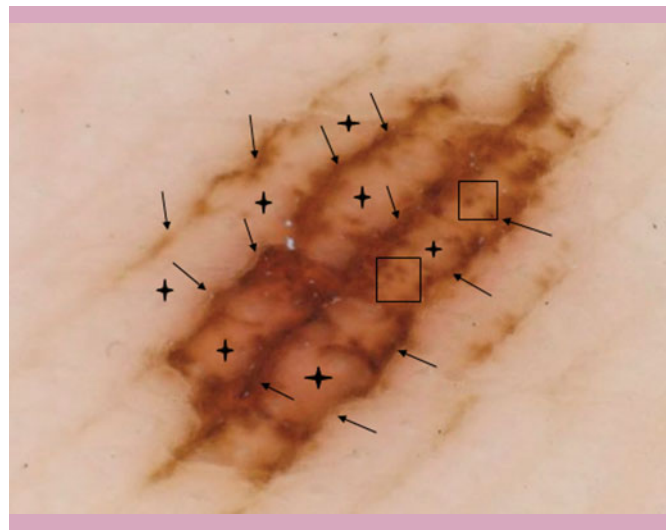


FIGURE 31-4 Acral nevus. This is a melanocytic lesion on acral skin with the benign parallel-furrow pattern. Pigmentation is in the thin furrows (arrows) with globules (boxes) in the ridges (stars).

- *Reticular pattern (benign)*
 - A lesion with only pigment network
- *Homogeneous pattern (benign)*
 - Brown homogeneous patch of color
- *Parallel-ridge pattern (thin/early melanoma)*
 - Pigmentation is in the thicker ridges of the skin (crista profunda intermedia) (Fig. 31-6)
 - Sometimes there are monomorphous round white structures in the ridges that represent the acrosyringia of the sweat ducts “string of pearls”

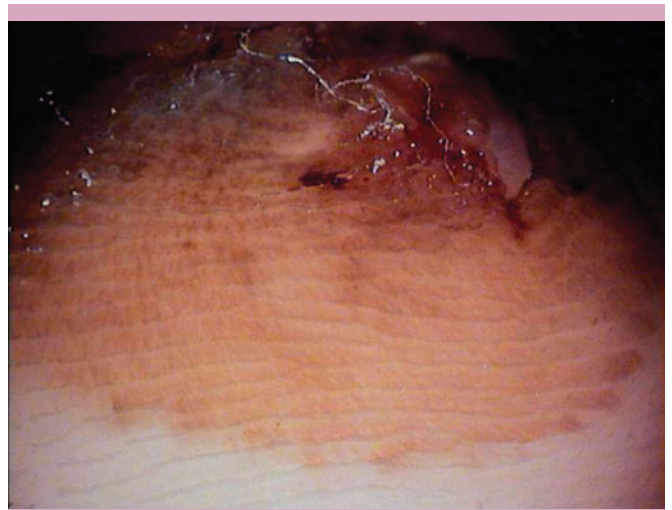


FIGURE 31-6 Acral melanoma. The parallel-ridge pattern diagnoses this acral melanoma with pigmentation in the thicker ridges (black arrows). The thin white lines are the furrows (yellow arrows).

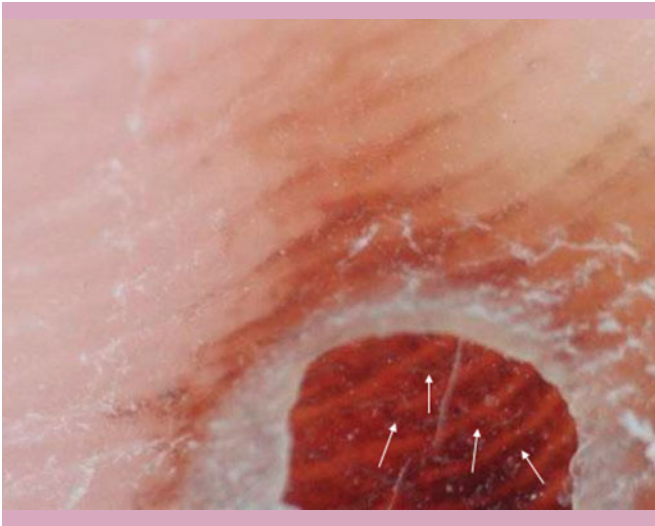


FIGURE 31-7 Acral hemorrhage. The parallel-ridge pattern created by blood (white arrows).

- Parallel ridge pattern created by blood (talon noir) (Fig. 31-7)
- Parallel ridge pattern in darker skinned races (Fig. 31-8)
- Macules seen in the Peutz-Jegher's syndrome
- This pattern is not 100% diagnostic of melanoma
- *Diffuse variegate pattern (melanoma)*
 - Pigmented blotches
 - Black, brown or gray
- *Multicomponent pattern (melanoma)*
 - Filled with regular and irregular criteria
 - Multiple colors plus areas with acral patterns (fibrillar, parallel-furrow)
- *Non-specific pattern (melanoma)*
 - If one cannot determine any of the above benign or malignant patterns; this represents a "red flag" of concern

Pearls

- There can be exceptions to every dermoscopic rule
- The history and clinical appearance of the lesion are important and should not be ignored
- If a pigmented lesion on the soles is rapidly changing yet has a typical benign parallel furrow pattern, it still could be melanoma
- A supposedly benign acral pattern with irregularity to the components could be high risk
- The presence of blood at acral sites (palms, soles, nails) may or may not be associated with melanoma
- Look carefully for other important criteria
- If in doubt, cut it out!

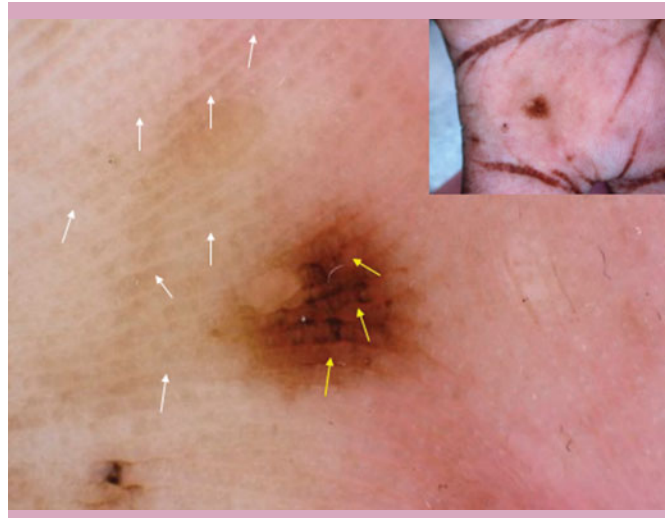


FIGURE 31-8 Acquired nevus. There is an increased incidence of acral melanoma in darker skinned races. This nevus on the palm of an African - American was without change and demonstrates the benign parallel-ridge pattern. Pigmentation is seen in the ridges of the nevus (yellow arrows) and in the ridges of the entire palm (white arrows).

- *Seborrheic keratosis*
 - *Milia-like cysts*
 - Various sized white or yellow structures
 - Small or large, single or multiple
 - They can appear opaque or bright like "stars in the sky" (epidermal horn cysts)
 - *Follicular openings/ pseudofollicular openings/ comedo-like openings*
 - Sharply demarcated roundish structures
 - Pigmented or nonpigmented
 - Shape can vary, not only within a single lesion, but from lesion to lesion in an individual patient or in different patients
 - When pigmented, they can be brownish-yellow or even dark brown and black (keratin-filled invaginations of the epidermis)
 - Pigmented follicular openings can be hard to differentiate from the pigmented dots and globules of a melanocytic lesion (Fig. 31-9)
- *Fissures and ridges*
 - Fissures (sulci/crypts) and ridges (gyri) seen in papillomatous seborrheic keratosis can create several patterns
 - ▲ Cerebriform or brain-like in which they resemble a sagittal section through the cerebral cortex
 - ▲ Mountain-like with variously sized or uniformly roundish structures representing mountains (ridges) and fine pigmented lines representing valleys (fissures)

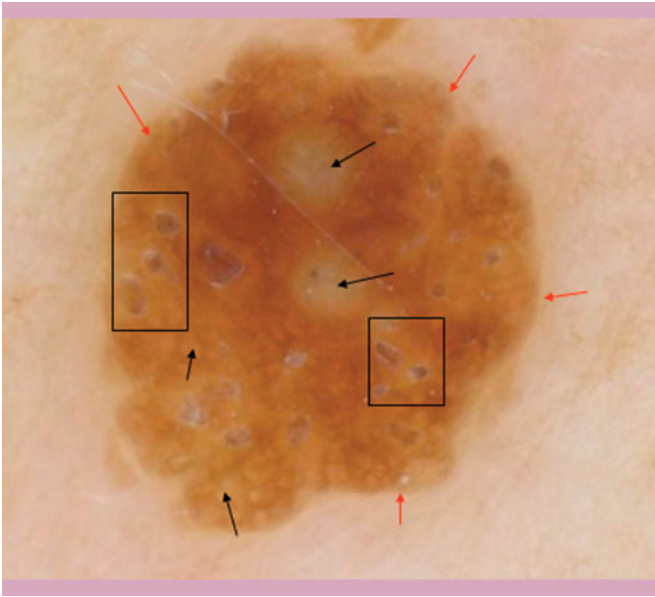


FIGURE 31-9 Seborrheic keratosis. Sharp borders (red arrows) milia-like cysts (black arrows) and follicular openings (boxes) characterize this seborrheic keratosis.

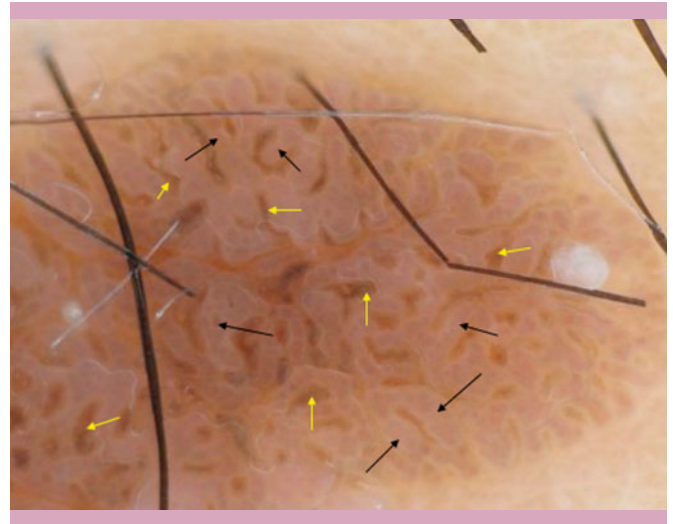


FIGURE 31-10 Seborrheic keratosis. A striking brain-like pattern created by pigmented fissures (yellow arrows) and light ridges (black arrows). Many of the ridges look like “fat fingers.”

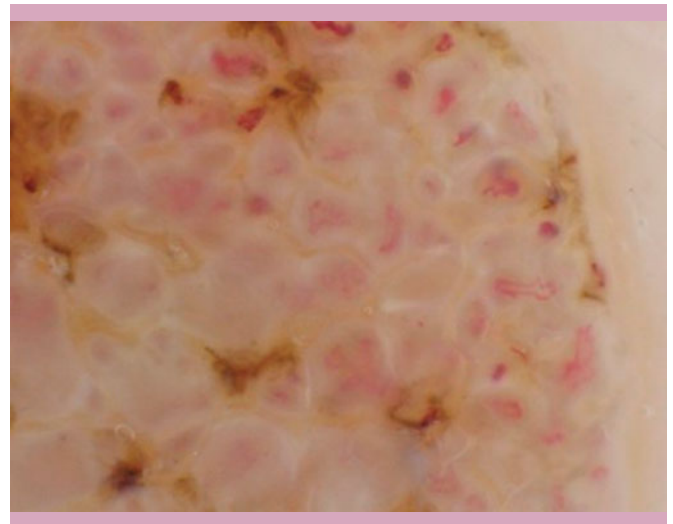


FIGURE 31-11 Seborrheic keratosis. An especially well formed hairpin vessel (box) in a seborrheic keratosis.

- △ Possible to confuse the mountain and valley pattern with the cobblestone pattern of a melanocytic lesion
 - ▲ Pigmented lines should not be confused with an atypical pigment network
 - ▲ Hypo- and hyperpigmented ridges can be digit-like (straight, kinked, circular or branched) and are referred to as “fat fingers”
- All of these patterns are commonly seen in this ubiquitous benign skin lesion (Fig. 31-10)
- *Fingerprint pattern*
 - Brown fine/thin parallel line segments that resemble fingerprints
 - Differ from the pigment network where the line segments are honey comb-like or reticular
 - Fingerprint pattern can be seen in flat seborrheic keratosis or in solar lentigines
 - Some authors believe that solar lentigines are flat seborrheic keratosis (see below and Fig. 31-23)
- *Hairpin vessels*
 - Elongated vessels (capillary loops) resembling hairpins (Fig. 31-11)
 - May or may not be surrounded by hypopigmented halos
 - Light halo indicates a keratinizing tumor and may be found in keratoacanthomas
 - Irregular and thick hairpin vessels can be seen in melanoma
- *Moth-eaten borders*
 - Flat or slightly raised brown seborrheic keratoses
 - Well demarcated, concave borders that are felt to resemble a “moth-eaten” garment
- *Sharp demarcation*
 - The majority of seborrheic keratoses have sharp, well-demarcated borders
 - Not always indicative of melanoma in a pigmented lesion (Fig. 31-9)
- Basal cell carcinoma
 - Absence of the criteria seen in a melanocytic lesion
 - ▲ Specifically, absence of a pigment network

- ▲ Dots and globules plus homogeneous blue color found in some basal cell carcinomas
- ▲ Raises the issue of dermoscopic differential diagnosis of individual criterion
- *Arborizing vessels*
 - One of the most sensitive and specific vascular structures seen with dermoscopy
 - ▲ Red tree-like branching telangiectatic blood vessels
 - ▲ Can be thick or thin lines that are in focus because of their superficial location
 - ▲ Most often there are different caliber vessels in a single lesion
 - Can also be found in
 - ▲ Benign nevi
 - ▲ Sebaceous gland hyperplasia
 - ▲ Scars
 - ▲ On sun-damaged skin
 - ▲ Melanoma
- *Pigmentation*
 - Basal cell carcinoma may or may not contain pigment (pigmented nests or island of basal cell carcinoma in the dermis) that can range from
 - ▲ Fine dots to large leaf-like structures (bulbous extensions forming a leaf-like pattern)
 - ▲ Blue-gray ovoid nets
 - ▲ Multiple blue-gray globules
- ▲ Colors that can be seen
 - △ Black
 - △ Brown
 - △ Gray
 - △ Blue
 - △ Red
 - △ White
- Not necessary to try to determine if “leaf-like” structures (“maple leaf-like areas”) are present since in reality this is a difficult task (Fig. 31-12)
- *Ulceration*
 - Single or multiple areas where there is loss of epidermis with oozing blood or congealed blood and crusts (Fig. 31-13)
 - There should be no recent history of trauma
- *Spoke-wheel structures*
 - Spoke-wheel structures are the only criterion with dermoscopy that are 100% diagnostic
 - ▲ Can be found in up to 10% of basal cell carcinomas
 - ▲ May or may not be associated with the other criteria used to make the diagnosis
 - Well-defined pigmented radial projections meeting at a darker central globule/central axle/hub
 - Complete or incomplete variations of this structure can be seen and one often has to use their imagination to make the identification
 - Finding spoke-wheel structures might be the only clue to the correct diagnosis

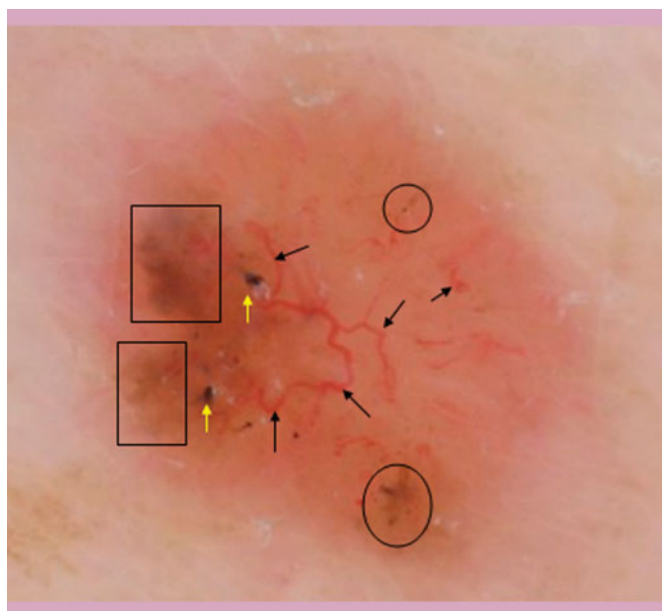


FIGURE 31-12 Basal cell carcinoma. This pigmented basal cell carcinoma has classic arborizing vessels (black arrows), gray blotches (boxes), blue globules (yellow arrows) and fine gray dots (circles). The three different presentations of pigmentation point out how variable this criterion can be.

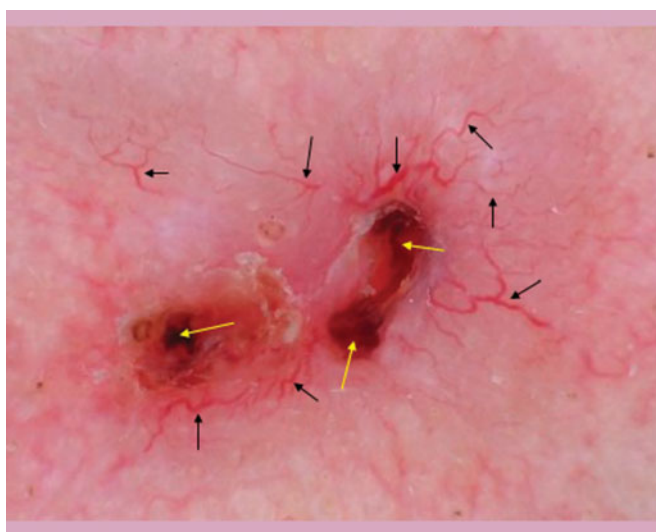


FIGURE 31-13 Basal cell carcinoma. Arborizing vessels (black arrows) and ulceration (yellow arrows) characterize this nonpigmented basal cell carcinoma.

Pearl

- A nonhealing area in an adult that bleeds spontaneously is a basal cell carcinoma until proven otherwise

- Dermatofibroma
 - *Central white patch*
 - Most typical presentation of this criterion is:
 - ▲ Centrally located
 - ▲ Scar-like
 - ▲ Bony or milky white
 - ▲ Homogeneous area (scarring in this fibrohistiocytic tumor)
 - Several variations such as white network-like structures (negative pigment network, reticular depigmentation) which can also be seen in Spitz nevi and melanoma
 - Telangiectatic vessels with different shapes can also be found anywhere in the lesion
 - Not all dermatofibromas have a central white patch
 - The clinically firm feel should be used to help make the diagnosis
 - *Pigment network*
 - Dermatofibromas are one of the nonmelanocytic lesions that can have a pigment network; solar lentigines are another
 - ▲ In most cases, a fine peripheral pigment network with thin brown lines is seen
 - ▲ Not all dermatofibromas have a pigment network

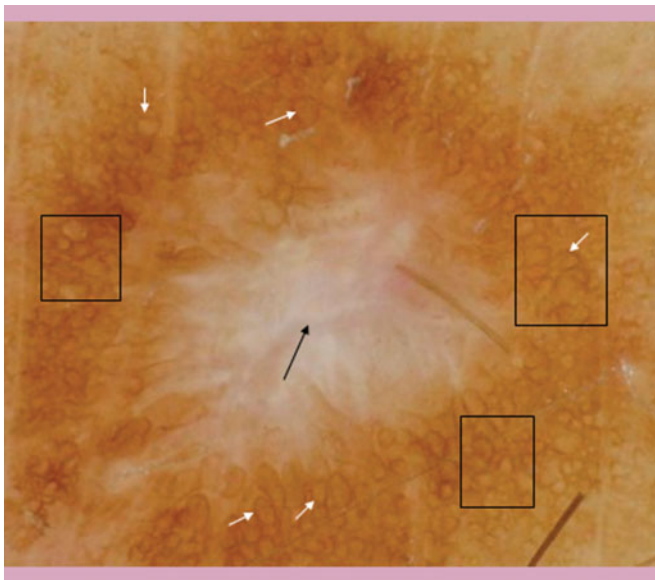


FIGURE 31-14 Dermatofibroma. A classic central white patch (black arrow) and pigment network (black boxes) characterize this dermatofibroma. In this instance, ring-like structures (white arrows) make up the pigment network.

- ▲ Ring-like structures which are a variation of a hyperpigmented network (Fig. 31-14)
- Atypical dermatofibromas with the following features are melanoma mimics that warrant a histopathologic diagnosis:
 - ▲ Irregular pigment network
 - ▲ Irregular dots/globules/ blotches
 - ▲ Pink color
 - ▲ Irregular regression-like white color
 - ▲ High-risk vascular structures (Fig. 31-15)
- Vascular lesions
 - *Lacunae/lagoons/sacculles*
 - Sharply demarcated bright red to bluish round or oval structures (dilated vascular spaces in the dermis) (Fig. 31-16)
 - ▲ Different colors can be seen in a single hemangioma
 - ▲ Lacunae should not be mistaken for the milky-red color seen in pigmented and amelanotic melanoma which can have “out-of-focus” reddish globular-like structures
 - ▲ Black homogeneous structureless areas represent thrombosis
 - ▲ Significant scale or dryness (hyperkeratosis) can be seen in angiokeratomas
 - Patchy white color or blue-white veil (blue and or white color) is commonly seen in hemangiomas

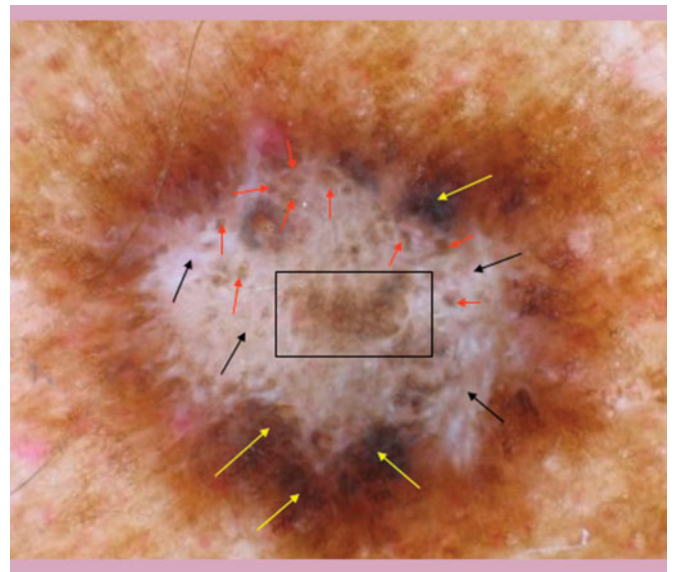


FIGURE 31-15 Atypical dermatofibroma. Regressive melanoma is in the dermoscopic differential diagnoses of this atypical dermatofibroma. There is asymmetry of color and structure, the multicomponent global pattern, irregular pigment network (box), irregular globules (red arrows) and irregular blotches (yellow arrows). This warrants a histopathologic diagnosis.

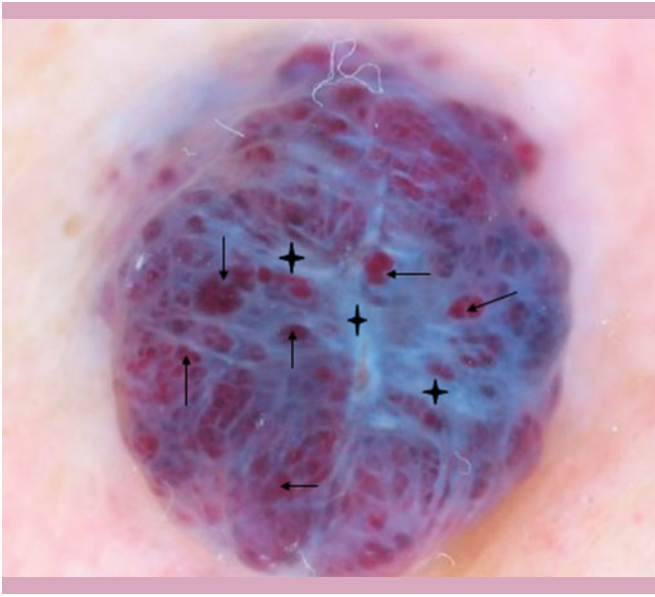


FIGURE 31-16 Hemangioma. Well-demarcated dark red lacunae (arrows) and blue-white color (stars) characterize this classic hemangioma.

- It should not be mistaken for the scar-like white color of regression or the blue color that can be found in melanomas
- Cutaneous metastatic melanoma can be indistinguishable from a hemangioma
 - ▲ A history of a previous melanoma will help make the diagnosis (Fig. 31-17)

Pearl

- There is a significant learning curve with dermoscopy. It is essential to learn the definitions of the basic criteria and patterns and be able to recognize the classic examples because there are innumerable variations that one will see in daily practice. This is a monumental weak link in the chain for those who attempt to master this tissue-sparing and life-saving technique

STEP TWO: Analysis of a Melanocytic Lesion

PATTERN ANALYSIS DEFINED

Identify as many criteria in the lesion as possible and see if they fit into the known patterns associated with the variants of

- Melanocytic Nevi
 - Congenital
 - Acquired
 - Recurrent
 - Halo
 - Combined

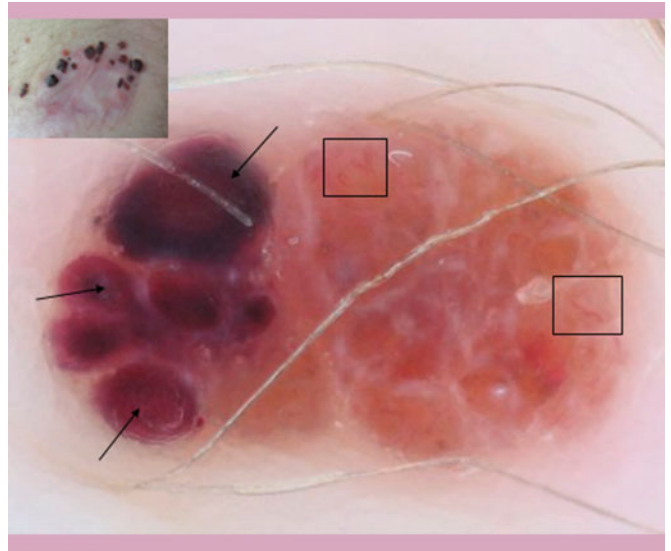


FIGURE 31-17 Cutaneous metastatic melanoma. This is one of many generalized cutaneous metastatic lesions in a 27-year-old white male with a history of a 7 mm melanoma on his back. There are well-demarcated lacunae-like areas (arrows) and atypical vessels (boxes). A collision lesion, hemangioma and amelanotic melanoma is in the dermoscopic differential diagnosis.

- Blue
- Dysplastic
- Spitz
- Melanoma
 - In situ
 - Superficial spreading
 - Nodular
 - Amelanotic
 - Nail apparatus
 - Acral
- Even though pattern analysis is considered a melanocytic algorithm, the same principles are used to diagnose all of the lesions that can be identified with the technique
 - Melanocytic
 - Nonmelanocytic
 - Benign
 - Malignant
 - Inflammatory

Pearls

- Do not focus on one or two criteria and make a diagnosis before checking for all the criteria. You could be lead astray
- Try to identify all of the criteria in a lesion
- High risk criteria that are present are not always easy to find. Beware!

PATTERN ANALYSIS METHOD

- *Step #1:*
 - Determine symmetry or asymmetry of color and or structure using the mirror image technique
 - Contour of the lesion is not important with this algorithm
 - The lesion is bisected by two lines that are placed 90 degrees to each other
 - The first line attempts to create the most symmetry as possible
 - Is the color and or the structure on the left half of the lesion a mirror image of the right half
 - Repeat the analysis for the upper and lower half of the lesion
 - Perfect symmetry of color and structure is not often found in nature, and inter observer agreement is not good with this assessment even among experienced dermoscopists
 - Symmetry or asymmetry can also be determined along any axis through the center of the lesion (Menzies method)
 - Significant asymmetry of color and or structure is a very important clue that you might be dealing with high risk pathology
 - Raise a “red flag” of concern and proceed with focused attention to what else you might find
- *Step #2:*
 - Determine the global/overall pattern of the lesion
The predominant criteria seen throughout the lesion could be:
 - Reticular
 - Globular
 - Cobblestone
 - Homogeneous
 - Parallel
 - Starburst
 - Multicomponent
 - Nonspecific
 - There can be combinations of criteria in a single lesion such as reticular and homogeneous or reticular and globular
 - The “reticular homogeneous pattern” or “reticular globular pattern”
- *Step #3:*
 - Identify the local criteria in the lesion:
 - Pigment network
 - Dots and globules
 - Streaks (also called pseudopods and radial streaming)
 - Blotches
 - Blue-white veil
 - Regression
 - Colors
 - Vascular structures

- *Step #4:*
 - Determine if the criteria seen are:
 - Regular or irregular (typical or atypical)
 - Good or bad
 - Low or high risk
 - Melanoma specific criteria are defined as criteria that can be seen in benign and malignant lesions but are more specific for high risk pathology such as:
 - Dysplastic nevi
 - Spitzoid lesions
 - Melanoma
 - All of the high risk criteria can be seen in benign pathology and one should never tell a patient that they have melanoma 100%
 - Due to the different characteristics of the skin in these locations the criteria are different on:
 - Trunk and extremities
 - Head and neck
 - Palms and soles
 - Thinner skin on the head and neck versus the trunk and extremities and thicker skin on the palms and soles with fissures and ridges
 - The criteria found on the head, neck, palms and soles are referred to as *site specific criteria* (Table 31-6)

GLOBAL PATTERNS

- *Reticular*
 - Pigment network filling most of the lesion
- *Globular*
 - Dots and globules filling most of the lesion
- *Cobblestone*
 - Larger angulated globules resembling street cobblestones filling most of the lesion (Fig. 31-18)
- *Homogeneous*
 - Diffuse pigmentation in the absence of local criteria such as pigment network, dots and globules
- *Starburst (Spitzoid)*
 - Streaks and/or dots and globules at the periphery of the lesion
- *Multicomponent*
 - Three or more different areas within a lesion
 - Each zone can be composed of a single criterion or multiple criteria
- *Nonspecific*
 - None of the above global patterns can be identified

LOCAL CRITERIA

- *Regular (typical) pigment network:*
 - Various shades of brown
 - Honeycomb-like (web-like, reticular) line segments
 - Uniform color, thickness and holes

TABLE 31-6 Melanoma-Specific Criteria in Different Body Regions

Trunk and Extremities	Head and Neck	Palm and Soles	Nail Apparatus
<p>Global criteria:</p> <p>Asymmetry of color and or structure</p> <p>Multicomponent pattern</p> <p>Non-specific pattern</p> <p>Local criteria: Irregular pigment network</p> <p>Irregular dots and globules</p> <p>Irregular streaks (pseudopods/radial streaming)</p> <p>Irregular blotches</p> <p>Blue-white veil</p> <p>Regression</p> <p>5 or 6 colors</p> <p>Atypical vascular pattern (vessels associated with melanoma)</p>	<p>Asymmetrical pigmentation around follicular openings</p> <p>Annular granular structures/pattern</p> <p>Rhomboid structures</p> <p>Dark homogeneous areas</p>	<p>Parallel ridge pattern</p> <p>Diffuse variegate pigmentation</p> <p>Multicomponent pattern</p> <p>Atypical reticulated/lattice-like pattern</p> <p>Non-specific pattern</p>	<p>Loss of parallelism of pigmented bands/melanonychia striata</p> <p>Hutchinson and Micro-Hutchinson's sign</p>

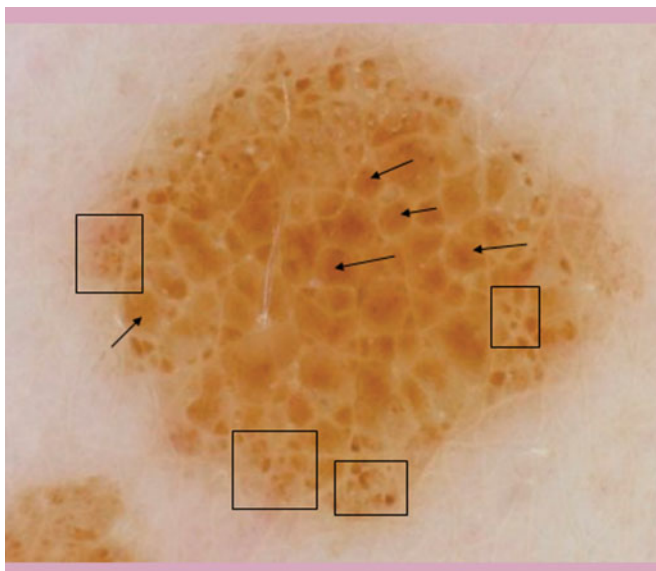


FIGURE 31-18 Acquired nevus. Small dots and globules (boxes) and larger angulated globules (arrows) characterize this benign nevus. The mountain and valley pattern seen in seborrheic keratosis is in the dermoscopic differential diagnosis. A positive wobble sign in which the soft nevus moves from side to side with movement of instrumentation versus a stiff immovable seborrheic keratosis helps to make the differentiation.

- *Irregular (atypical) pigment network:*
 - Black, brown or gray
 - Line segments that are thickened, branched and broken up (enlarged, fused rete ridges)
 - There may be a diffuse distribution or foci of irregular pigment network
- *Regular dots and globules:*
 - Brown roundish structures
 - Usually clustered
 - Dots (0.1 mm) are smaller than globules (greater than 0.1 mm)
 - Size, shape and color are similar with an even distribution in the lesion (nest of melanocytes at the dermo epidermo junction)
 - Dots and/or globules only found at the periphery can be seen in Spitz or actively changing nevi
 - Actively changing means if followed digitally the nevus will invariably enlarge within a short period of time
 - Peripheral dots and globules are usually seen in younger patients with benign pathology
 - Beware of this pattern in a newly acquired nevus in an adult
- *Irregular dots and globules:*
 - Black, brown, gray or red roundish structures
 - Different sizes and shades of color

- Usually but not always asymmetrically located in the lesion
- *Regular streaks:*
 - Black or brown linear projections of pigment
 - Can be associated with a pigment network but most often are not
 - At all points along the periphery of the lesion
 - Pseudopods and radial streaming are similar structures clinically and histopathologically (aggregates of tumor cells running parallel to the epidermis that can be seen in Spitz nevi or represent the radial growth phase of melanoma) that are difficult to differentiate from each another
 - To simplify the identification, the term “streaks” is now used by many but not all experienced dermoscopists to encompass all variations of this criterion
 - The shape of the linear projections does not determine if they are regular or irregular, rather their distribution at the periphery of the lesion
- *Irregular streaks:*
 - Black or brown linear projections
 - Can be associated with a pigment network but most often are not
 - Irregularly distributed at the periphery of a lesion
 - Some but not all points at the periphery, foci of streaks
- *Regular blotches:*
 - Black, brown or gray
 - Structureless (i.e., absence of network, dots or globules) areas of color
 - Bigger than dots and globules
 - Uniform shape and color symmetrically located in the lesion (aggregates of melanin in the epidermis and/or dermis)
- *Irregular blotches:*
 - Black, brown or gray structureless areas
 - Irregular in size and shape asymmetrically located in the lesion
- *Blue-white veil:*
 - Irregular, structureless area of confluent blue color
 - Overlying whitish ground glass appearance
 - Orthokeratosis
 - Acanthosis
 - Hypergranulosis
 - Heavily pigmented tumor cells in the dermis
- *Regression:*
 - Bony or milky white scar-like depigmentation (fibrosis)
 - With or without blue pepper-like granules:
 - Melanosis represents free melanin, melanophages
 - Atypical melanocytes in the dermis
- The white color should be lighter than the surrounding skin
- Regression by itself is an independently potentially high risk criterion
- The more regression seen, the greater the chance the lesion is a melanoma
- *Blue-white color:*
 - It is not always possible to identify classic regression on blue-white veil
 - Blue and/or white color of any intensity, shape or distribution
 - A “red flag” of concern should be raised
- *Hypopigmentation:*
 - Commonly seen featureless areas of light brown color in all types of melanocytic lesions both benign and malignant
 - Inexperienced dermoscopists can have trouble differentiating hypopigmentation from the white color seen with true regression
- *Colors seen with dermoscopy:*
 - Eumelanin has a brown color
 - Its location in the skin will determine the colors one sees with dermoscopy
 - Black indicates melanin is superficially located in the epidermis (i.e., in the stratum corneum)
 - Black is not always an ominous color but can be seen in benign pathology as well as in melanoma
 - Light and dark brown indicates pigment is at the dermo-epidermal junction
 - Gray in the papillary dermis represents free melanin and melanophages (“peppering”)
 - As the pigment gets into the deeper dermis it looks blue (the Tyndall effect)
 - Red and or pink color can be created by inflammation or neovascularization
 - Sebaceous material and hyperkeratosis can look yellow
 - The more colors seen, the greater chance one is dealing with high risk pathology (Figs. 31-19, 31-20, 31-21)
- *Atypical vascular pattern/polymorphous vascular pattern:*
 - Vessels that can be seen in melanoma are nonspecific; they can also commonly be found in other lesions including
 - Benign
 - Malignant
 - Inflammatory
 - When identified they should raise a “red flag” of concern including
 - Dotted/pinpoint (dots resembling the head of a pin)

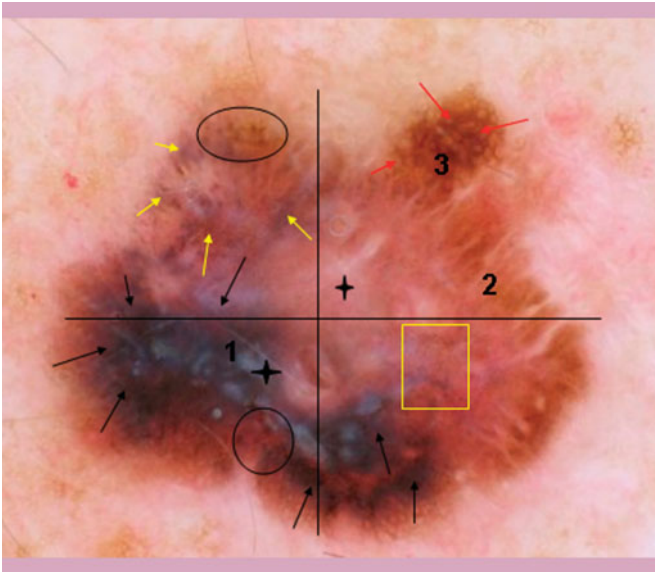


FIGURE 31-19 Melanoma. This is a melanocytic lesion because there is a pigment network (red arrows) and aggregated globules (circles). There is asymmetry of color and structure (+) plus the multicomponent global pattern (1,2,3). Local criteria includes; irregular pigment network (red arrows), irregular dots and globules (circles), irregular blotches (black arrows) and blue-white color (stars). The classic blue-white veil is not seen. Peppering (yellow box) and gray blotches (yellow arrows) are part of the regression. More than five colors are seen including red.

- Irregular linear
- Irregular tortuous/corkscrew (irregular, thick, coiled)
- Irregular hairpin (irregular and thick hairpin shaped)
- Glomerular
- One must focus his/her attention to make out the shapes of these small vessels (Fig. 31-22)
- *Milky-red areas:*
 - Localized or diffuse (amelanotic melanoma) pinkish-white color
 - With or without reddish and or bluish out of focus/ fuzzy globular structures (neovascularization)
 - Not to be confused with the in focus lacunae seen in hemangiomas
- *Glomerular vessels:*
 - Diffuse or clustered fine coiled vessels that can be seen in
 - Bowen disease (Fig. 31-22)
 - Melanoma
 - Pink lichen planus – like keratosis
 - Stasis dermatitis
 - Psoriasis

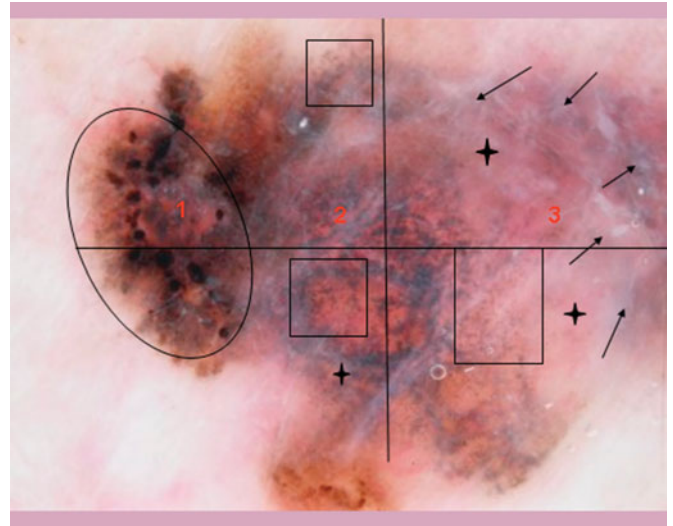


FIGURE 31-20 Melanoma. There is a melanocytic lesion because there are aggregated globules (circle). There is asymmetry of color and structure (+) plus the multicomponent global pattern (1,2,3). Local criteria includes; irregular dots and globules (circle), blue-white color (stars) and peppering (boxes). The classic blue-white veil is not seen. More than five colors, including red, are another melanoma specific criterion.

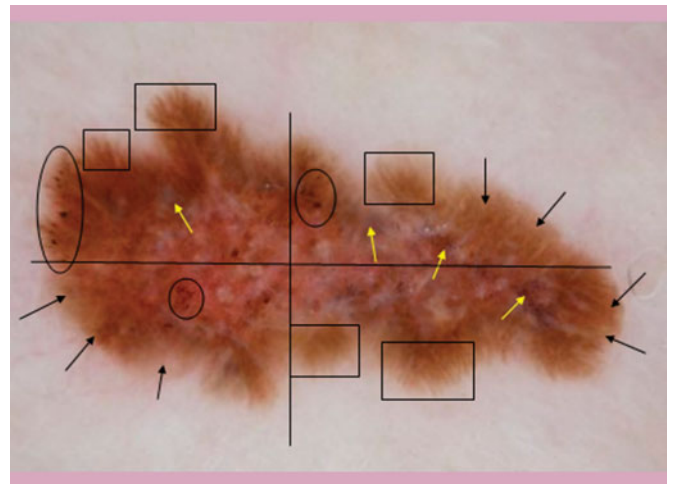


FIGURE 31-21 Melanoma. This is a melanocytic lesion because there are aggregated globules (circles). There is an atypical starburst (spitzoid) global pattern with foci of streaks at the periphery (boxes). Local criteria includes; irregular dots and globules (circles), irregular streaks (boxes) and regression. The white and gray blotches (yellow arrows) make up the regression. The black arrows point out where there are no streaks. Five colors, including red, round off the melanoma specific criteria.



FIGURE 31-22 Bowen disease. Typical glomerular vessels (black box) and large dotted vessels (yellow box) help diagnose this nonspecific pink scaly patch.

- *Asymmetrical pigmentation around follicular openings:*
 - Seen only on the head and neck
 - Irregular brown color outlining parts of the round follicular openings
 - The color does not completely encircle the openings (early proliferation of atypical melanocytes)
- *Annular-granular pattern/structures:*
 - Seen only on the head and neck
 - Brown or gray fine dots that surround follicular openings (melanophages and or atypical melanocytes)
 - This criterion can be seen in
 - Lentigo maligna, lentigo maligna melanoma
 - Pigmented actinic keratosis
 - Post traumatic
 - Late stage lichen planus-like keratosis (Figs. 31-23, 31-24)
- *Rhomboid structures:*
 - Seen only on the head and neck
 - Rhomboid is a parallelogram with unequal angles and sides
 - Black, brown, or gray thickening around the follicular openings
 - In reality true rhomboids are not regularly formed
 - Any pigmented thickening around follicular openings is worrisome
- *Dark homogeneous areas:*
 - On the head and neck
 - Irregular in size and shape
 - Black or brown homogeneous blotches of color

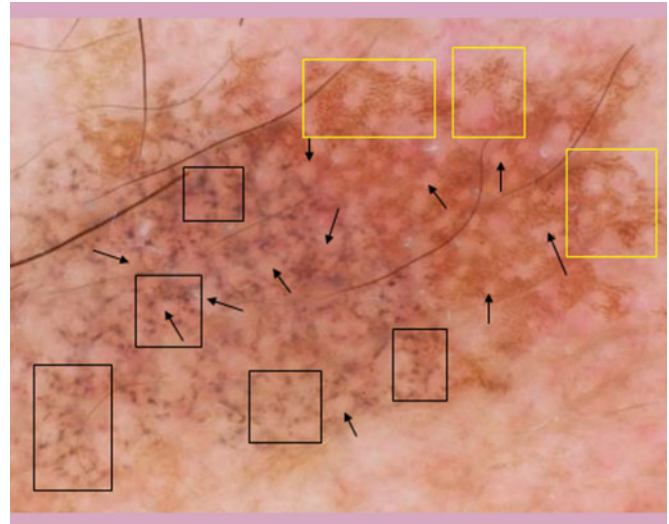


FIGURE 31-23 Lichen planus-like keratosis. Remnants of a fingerprint pattern (yellow boxes) of a flat seborrheic keratosis and the gray annular-granular pattern (black boxes) around follicular openings (arrows) are the clues that this is not lentigo maligna. The gray dots represent melanophages and free melanin in the papillary dermis, not atypical melanocytes. A sub-set of lichen planus-like keratosis are thought to represent an immunologic event against flat seborrheic keratosis of solar lentigines.

- Complete occlusion of follicular openings due to invasive melanoma (lentigo maligna melanoma)

Pearls

- Actinic keratosis and actinic lentigines can be associated with lentigo-maligna on the head and neck
- Use the areas where the high risk criteria are located to perform a biopsy, or the malignant diagnosis could be missed. There should be a good dermoscopic-pathologic correlation
- If you think the lesion is lentigo maligna yet the pathology report does not make the diagnosis, seek another histopathologic opinion or biopsy another area of the lesion
- *Benign pigmented nail bands (melanonychia striata):*
 - Single or multiple nail involvement with brown longitudinal parallel lines
 - Uniform color, spacing and thickness
 - A single band in a lighter skinned person with these findings is still worrisome
- *Malignant pigmented nail bands (atypical melanonychia striata):*
 - Loss of parallelism with brown, black, or gray

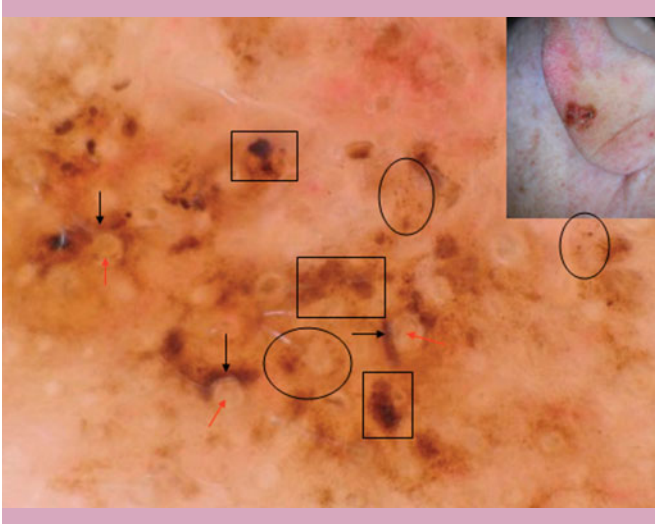


FIGURE 31-24 Lentigo maligna (ear lobe). This case demonstrates variations of the classic criteria. The lesion is suspicious clinically but has a differential diagnosis that includes a seborrheic keratosis. The dermoscopic criteria for a seborrheic keratosis are not present. There is asymmetry of color and structure, asymmetrical pigmentation (black arrows) around follicular openings (red arrows), annular-granular structures (circles) and irregular blotches (boxes). One should have a mental checklist of the melanoma-specific criteria for the head and neck because they are not always easy to find and identify.

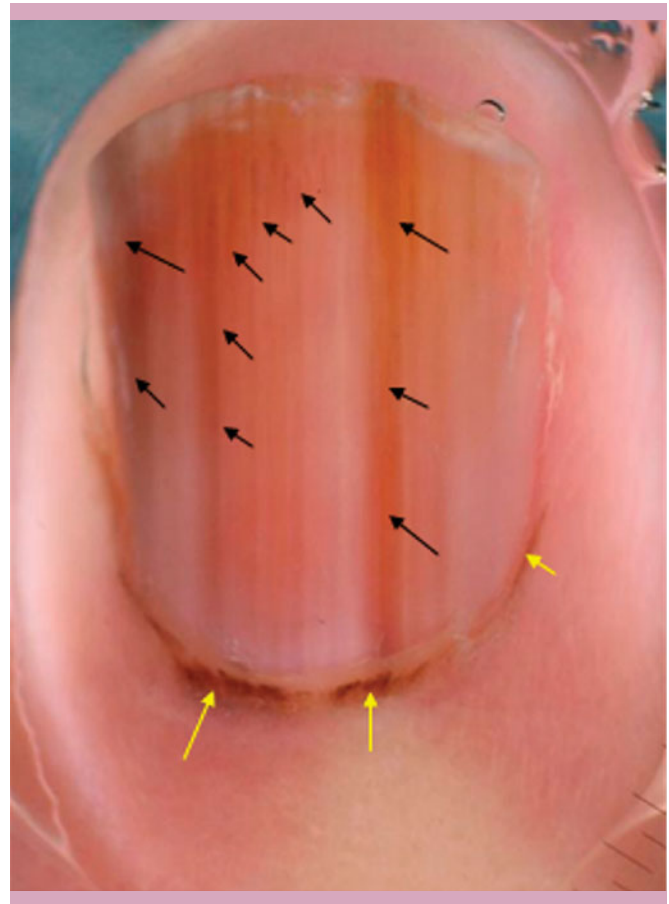


FIGURE 31-25 Acrolentiginous Melanoma/Nail Apparatus Melanoma. The pigmented bands are not uniform in color and thickness (black arrows). There is also Hutchinson's sign (yellow arrows). (Courtesy of Wilhelm Stolz, MD.)

parallel lines that demonstrate different shades of color, irregular spacing and thickness (Fig. 31-25)

- High risk dermoscopic criteria at this location in adults are usually not associated with high risk pathology when seen in children
- Disfiguring nail matrix biopsies can usually be avoided
- Any rapidly changing scenario warrants a histopathologic diagnosis no matter how old or young the patient
- Digital monitoring is helpful to monitor pigmentation in the nail apparatus
- *Micro-Hutchinson's sign: Hutchinson's sign*
 - Pigmentation of the cuticle that can only be seen clearly with dermoscopy
 - Pigmentation of the cuticle easily seen without dermoscopy
- *Non-melanocytic nail apparatus bands:*
 - Uniform grayish lines on a gray background can be seen in lentigo
 - Drug induced pigmentation multiple nails involved

- Darker skinned races multiple nails involved
- *Nail-apparatus blood/subungual hematoma:*
 - The color of blood seen in the nail apparatus depends how long the blood has been there
 - Fresh blood looks red or purple/violaceous
 - Older blood can look yellowish brown or black
 - A well demarcated homogeneous area with parallel lines at the distal edge and globule-like blood spots/pebbles (Fig. 31-26)
 - Digital dermoscopy is helpful to follow nail apparatus blood that should slowly move distally over several months

Pearls

- Presence of blood in a nail does not rule out melanoma
- Search carefully for high risk criteria that might also be present

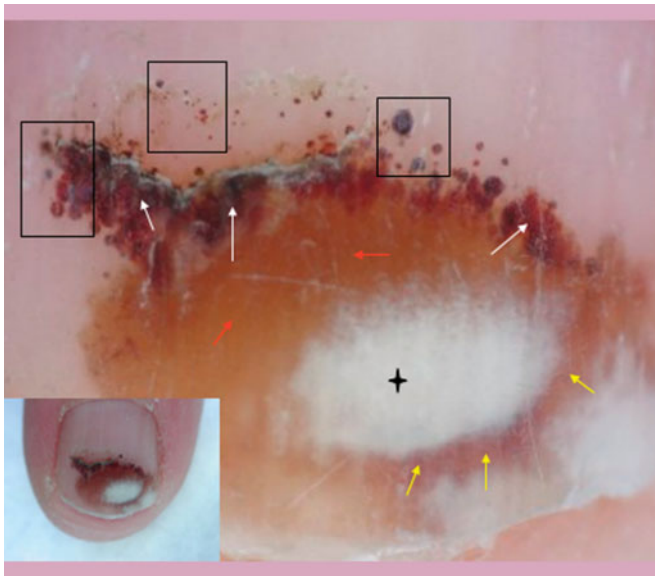


FIGURE 31-26 Sub-ungual hematoma. Different colors plus blood pebbles (boxes) characterize this posttraumatic lesion. The white color (star) is secondary to trauma not regression. The brown (red arrows) and purple blotches (white arrows) result from the breakdown of blood. No melanoma specific criteria are seen.

- Finding the Hutchinson's sign and the parallel-ridge pattern on the surrounding skin adjacent to the nail can help make the diagnosis of nail apparatus melanoma

COMMON DERMOSCPIC PATTERNS

- *Congenital nevi:*
 - Diffuse homogeneous brown color
 - Patchy or diffuse pigment network (target network may or may not be seen as network holes each with a small centrally located brown dot or pinpoint vessel)
 - Globular and/or cobblestone pattern (target globules may or may not be seen as globules with a smaller centrally located dot or vessel)
 - Islands of normal skin and islands of criteria such as network dots and globules
 - Multicomponent pattern with three or more distinct areas of criteria
 - Dark coarse terminal hairs (hypertrichosis) with or without surrounding hypopigmentation (perifollicular hypopigmentation) (Fig. 31-27)
 - Milia-like cysts and follicular openings most often found in seborrheic keratosis can be seen
- *Acquired nevi:*
 - Light/dark brown or pink color
 - Regular pigment network
 - Lacks sharp demarcation at the borders
 - Globular or cobblestone pattern (the most common pattern seen in children)

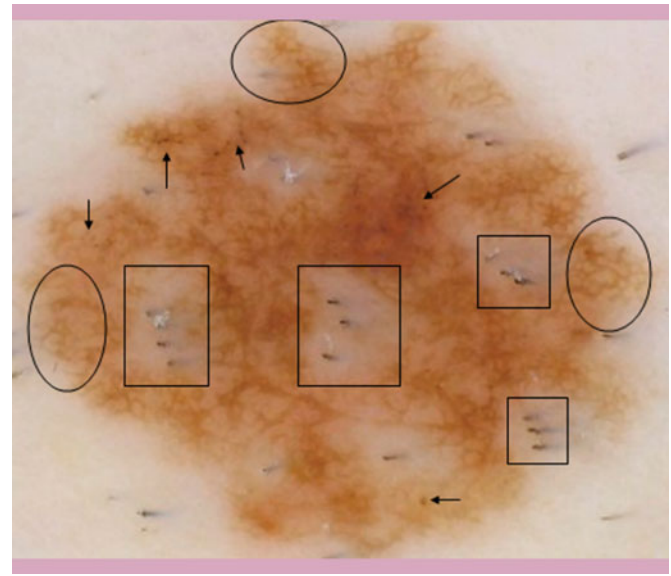


FIGURE 31-27 Congenital melanocytic nevus. Terminal hairs with perifollicular hypopigmentation (boxes), atypical pigment network (circles) and regular globules (arrows) characterize this small congenital melanocytic nevus.

- Symmetry of color and structure
- Comma-shaped blood vessels
- Hypopigmentation
- Milia-like cysts and follicular openings can be seen
- Pink nevi can be featureless or feature poor
- A solitary flat pink lesion is more worrisome than multiple soft and compressible pink lesions

Pearl

- Dermoscopy might not be helpful to diagnose pink macules and papules which can be melanocytic, nonmelanocytic, benign, malignant or inflammatory (Fig. 31-28)

- *Blue nevi:*
 - Blue, blue-gray or blue-black homogeneous color (Fig 31-3)
 - Variable number of subtle blue globular-like structures
 - Regression with white or gray areas commonly seen
 - Radiation tattoo, nodular and metastatic melanoma is in the dermoscopic
 - differential diagnosis
 - The history is essential to make the differential diagnosis
- *Combined nevi:*
 - Light or dark brown homogeneous color + /- other local criteria (regular nevus) and central

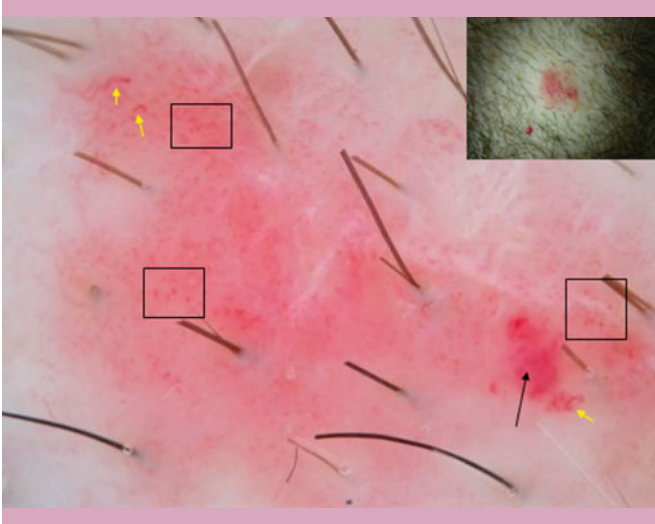


FIGURE 31-28 Pink lichen planus-like keratosis. This small papule was only found after a complete skin examination. There are different shades of pink color, pinpoint (boxes) and comma shaped vessels (yellow arrows) plus a milky-red area (black arrow).

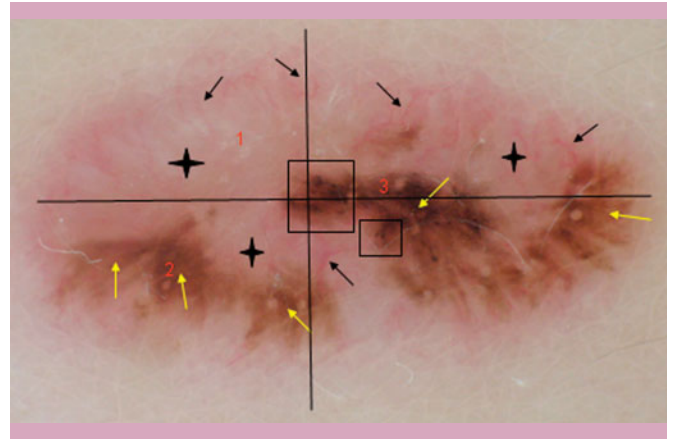


FIGURE 31-29 Recurrent nevus. Asymmetry of color and structure (+), the multicomponent global pattern (1,2,3) irregular globules (boxes), irregular blotches (yellow arrows), and scar tissue (stars) with arborizing vessels (black arrows) characterize this recurrent nevus.

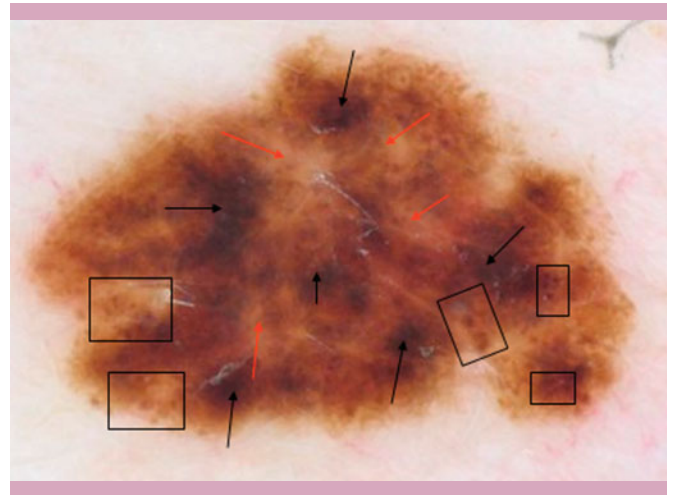


FIGURE 31-30 Dysplastic nevus. There are foci of irregular dots and globules (boxes), irregular blotches (black arrows) and multifocal hypopigmentation (red arrows).

- blue blotch (blue nevus) with a “fried egg” clinical appearance
- Diffuse brown homogeneous color with a blue border
- Diffuse blue homogeneous color with a brown border
- Variable combinations of blue and brown color
- *Recurrent nevi/pseudomelanoma*:
 - Sharp border
 - Irregular pigment network; irregular streaks
 - Irregular dots and globules
 - White scar-like areas with arborizing vessels
 - Any combination of criteria can be seen
 - Pigmentation centrally located in the scar; if the pigmentation goes out of the scar rule out melanoma
 - The history of previous surgery and histopathology is important (Fig. 31-29)
- *Dysplastic nevi*:
 - ABCDE clinical lesions can look banal or high risk with dermoscopy
 - Being indistinguishable from melanoma
 - Evolving/changing might be the only clue that a lesion is melanoma
 - Asymmetry of color and structure
 - Irregular pigment network
 - Irregular blotches
 - Irregular dots and globules
 - Multifocal hypopigmentation (Fig. 31-30)
 - Regression, blue-white color/ blue-white veil, atypical vessels and streaks are not usually seen

- Patients with multiple dysplastic nevi usually do not have many that look very atypical with dermoscopy
- Look for the clinical and/or dermoscopic “ugly duckling” to consider for biopsy or digital follow-up
- Pink dysplastic nevi can be feature poor or featureless with low or high grade histopathology

Pearl

- “Anything pink, stop and think!”

- An atypical starburst/spitzoid pattern with *foci* of dots/globules and/or streaks at the periphery can be seen in melanoma
- Symmetrical and asymmetrical starburst patterns can be seen in melanoma
- Homogeneous light brown or reddish featureless pattern
- Globular pattern with central blue-white color
- Diffuse black irregular pigment network pattern
- Atypical pattern similar to superficial spreading melanoma
- *Spitz nevi*:
 - There are six patterns seen in Spitz nevi
 - Starburst
 - Globular
 - Homogeneous
 - Pink
 - Black pigment network
 - Atypical
 - Spitzoid is the term used when any of the different six patterns is seen
 - Starburst is the most common pattern (Fig. 31-31)
 - Streaks and / or dots and globules at the periphery
 - Light /dark brown, black or blue color centrally

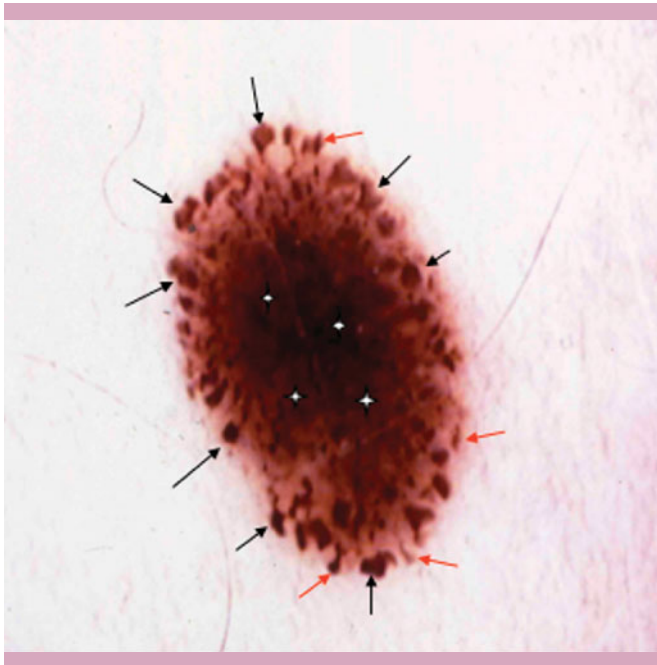


FIGURE 31-31 Spitz nevus. A central regular blotch (stars) plus globules (black arrows) and a few streaks (red arrows) at all points of the periphery characterize this classic starburst/spitzoid pattern.

- Regular or irregular pattern depends on the location of the streaks
 - ▲ Regular starburst pattern has symmetrical streaks around the lesion
 - ▲ Irregular starburst pattern has foci of streaks at the periphery
- Symmetrical and asymmetrical starburst patterns can be seen in melanoma
- Globular is the second most common Spitzoid pattern
 - Filled with regular or irregular dots/and or globules
 - Blue color seen centrally is the clue that the lesion might be a Spitz nevus
- Homogeneous pattern
 - Featureless brown color
- Pink pattern
 - Feature-less pink papule
- Black network pattern
 - The lesion is composed totally of a prominent black pigment network
 - Ink-spot lentigo and melanoma are in the differential diagnosis
- Atypical pattern
 - This can have any combination of melanoma-specific criteria
 - The histopathologic diagnosis is usually a surprise
- White pigment network/ negative pigment network/reticular depigmentation
 - This is an important clue that the lesion is Spitzoid

Pearl

- Any spitzoid pattern requires a histopathologic diagnosis especially in adults

- In-situ melanoma (trunk and extremities)
 - May or may not demonstrate the clinical ABCD clinical criteria
 - Flat or slightly raised lesion
 - Asymmetry of color and structure
 - Black and/or dark brown irregular pigment network
 - Irregular dots and globules
 - Irregular dark blotches
 - Hypopigmentation
 - Lacks the criteria for deeper melanoma (pink, red, gray or blue color, atypical vessels or regression)
 - Looks more malignant than benign but not definitely malignant (Fig. 31-32)
- *Superficial spreading melanoma*:
 - Starts in an existing nevus or de novo
 - Demonstrates the clinical ABCD criteria

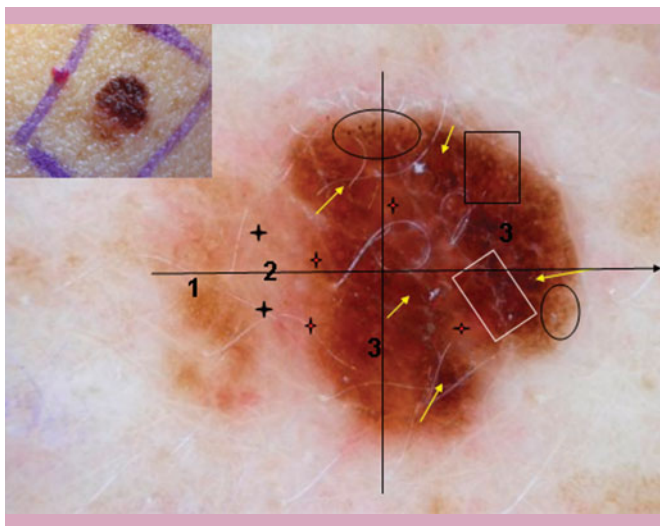


FIGURE 31-32 In-situ melanoma. This is a melanocytic lesion because there is a pigment network (black box) and aggregated globules (circles). There is asymmetry of color and structures (+), the multicomponent global pattern (1,2,3), irregular pigment network (black box), irregular dots and globules (circles), irregular blotches (yellow arrows), and reticular depigmentation (white box). The hypopigmentation (black stars) should not be confused with regression. There is diffuse erythema (red stars) and only three other colors.

- Contains a variable number of the melanoma specific criteria found on the trunk and extremities (Figs. 31-19, 31-20, 31-21)
- *Nodular melanoma:*
 - Starts in an existing nevus or de novo
 - May or may not be fast growing
 - Pigmented, hypomelanotic or amelanotic
 - Can be mistaken for benign nevus or squamous cell carcinoma
 - Usually lacks the clinical ABCD criteria
 - Due to the absence of the radial growth phase there is a scarcity of local criteria (network, globules, streaks)
 - Remnants of local criteria may or may not be present at the periphery of the lesion
 - Large intense dark blotches
 - Multiple deeper skin colors seen such as blue, white, pink, milky-red
 - Atypical vessels

Pearls

- The clinical appearance of a lesion (flat, palpable or nodular, presence or absence of the ABCD criteria) plus the colors and structures seen with dermoscopy can help

estimate if you are dealing with a thin, intermediate or thick melanoma

- Flat melanomas are usually in-situ with black and brown color plus well developed local criteria
- Thick melanomas tend to be elevated or nodular and can have a paucity or absence of local criteria such as pigment network, plus blue-white veil/color, multiple colors and the atypical vascular pattern

- *Amelanotic melanoma:*
 - Flat, palpable or nodular
 - Hypopigmented, pink or red
 - May or may not have the melanoma specific criteria typically seen in pigmented melanomas
 - Different shades of pink color and atypical vascular pattern
 - Milky-red areas are important clues to the correct diagnosis
 - Pediatric patients have a high proportion of amelanotic melanomas (Fig. 31-33)
 - Amelanotic melanoma should always be in the differential diagnosis of a pyogenic granuloma
- *Cutaneous metastatic melanoma:*
 - Dermoscopy might not be as helpful to make the diagnosis as the history of a melanoma being previously excised
 - Single or multiple
 - Pigmented or non-pigmented

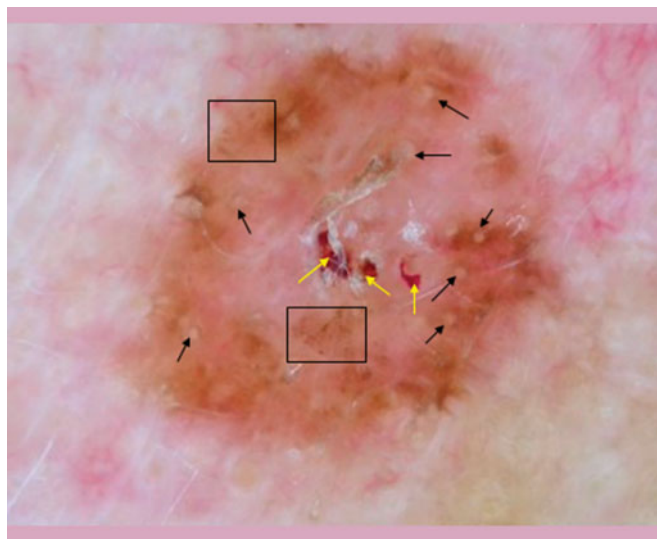


FIGURE 31-33 Amelanotic melanoma (feature poor melanoma). This is a melanocytic lesion because it has aggregated globules (boxes). There is an absence of melanoma specific criteria found on the face with different shades of pink and brown color plus ulceration (yellow arrows). Follicular openings (black arrows) should not be confused with the milia-like cysts of a seborrheic keratosis.

- All different sizes, shapes and colors can be seen in each patient with or without atypical vessels
- Any combination of criteria can be seen
- Benign patterns such as a hemangioma-like cutaneous metastatic melanoma (Fig 31-17)
- *Feature poor melanoma:*
 - Melanoma with subtle non diagnostic criteria (Fig. 31-33)
- *Featureless melanoma:*
 - Melanoma without dermoscopic criteria at all
- Melanoma incognito/false negative melanoma:
 - Clinically the lesion does not look like melanoma
 - With dermoscopy there are obvious or subtle clues to make the diagnosis
 - Clues to help make the diagnosis
 - History of dermoscopic change over time
 - A Spitzoid pattern in a lesion that does not look Spitzoid clinically
 - Areas of regression as the major high risk criterion
 - High risk vessels in a pink lesion
- The “*Little Red Riding Hood Sign*” is when the lesion looks clinically benign from a distance but not close up with dermoscopy

Pearl

- Dermoscopy should not only be used on clinically suspicious lesions if one wants to diagnose melanoma incognito

- *Nail apparatus melanoma:*
 - Amelanotic reddish diffuse color/amelanotic tumor
 - Diffuse melanonychia with different shades of black, brown or gray color
 - Irregular pigmented bands (Fig. 31-25)
 - A single uniform band does not rule out melanoma
 - Irregular dots and globules
 - Blood in 25% of lesions
 - Nail plate destruction with advanced disease
 - + /- Hutchinson sign
 - The parallel -ridge pattern can be seen on the adjacent skin
- *Ink spot lentigo:*
 - Black macule or macules on sun exposed areas
 - Prominent thickened black pigment network
 - Usually a very easy clinical and dermoscopic diagnosis
 - Melanoma could be in the clinical and dermoscopic differential diagnosis
 - Look for melanoma specific criteria that should not be present in an ink spot lentigo

- Solar lentigo:
 - Macules and/or patches
 - Different shades of homogeneous brown color
 - Moth-eaten concave borders
 - Fingerprint-like wavy linear line segments
- *Actinic keratosis:*
 - Nonpigmented actinic keratosis
 - Scaly surface
 - Pinkish-red pseudopigment network
 - Pigmented actinic keratosis
 - Mimics lentigo maligna
 - ▲ Asymmetrical follicular pigmentation
 - ▲ Annular-granular structures
 - ▲ Rhomboid structures

Pearl

- Multiple scaly lesions favors the diagnosis of actinic keratosis over lentigo maligna. Both can have pigmented and non-pigmented variants.

- Bowen’s disease (in situ squamous cell carcinoma):
 - Pink or reddish scaly macules, papules, patches, plaques
 - Pinpoint and/or glomerular vessels
 - Clusters and/or diffuse distribution of vessels throughout the lesion
 - With or without homogeneous brown color
- Keratoacanthoma:
 - Centrally located yellowish keratinous material
 - Peripheral whitish background
 - Hairpin vessels at the periphery
- Sebaceous gland hyperplasia:
 - Delled yellow papules seen clinically
 - Multiple grouped white or yellow globules
 - Small caliber basal cell carcinoma-like vessels
 - The vessels have been termed crown or wreath-like vessels
 - ▲ Supposedly never to reach the center of the lesion
 - ▲ This is a misnomer because in reality the vessels rarely meet this criterion and can be found anywhere in the lesion

Pearl

- The globules are the main feature used to differentiate sebaceous gland hyperplasia from basal cell carcinoma

- *Collision tumor:*
 - Lesion with the dermoscopic criteria for two different pathologies
 - One can find a triple collision lesion with three different pathologies

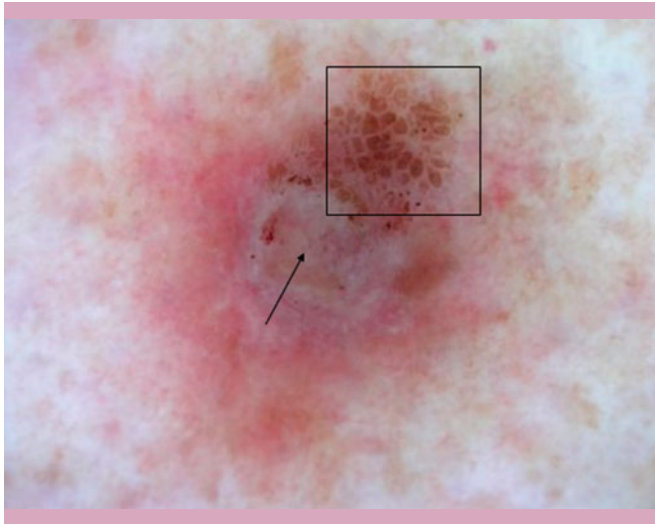


FIGURE 31-34 Collision tumor – squamous cell carcinoma and seborrheic keratosis. A rapidly growing nodule (arrow) representing a squamous cell carcinoma and the mountain and valley pattern of a seborrheic keratosis (box) characterize this lesion. The cobblestone pattern of a nevus is in the dermoscopic differential diagnosis.

- Collision tumors are commonly seen
- Diagnostic criteria can be side by side or one can be seen within the other
- Examples include:
 - Seborrheic keratosis, basal cell carcinoma
 - Seborrheic keratosis, in-situ or invasive squamous cell carcinoma
 - Seborrheic keratosis, amelanotic or pigmented melanoma
 - Seborrheic keratosis, eccrine porocarcinoma
 - Basal cell carcinoma, seborrheic keratosis, clear cell acanthoma
- Any combination is possible (Fig. 31-34)

OTHER DIAGNOSES MADE WITH DERMOSCOPY

Scabies

- Burrows appear as discrete linear areas
- Mites can be seen as a small triangle/gray delta structure that corresponds to the front section of the body with its mouth/biting apparatus and legs
- Higher magnification and oil increases the visibility of the mite, stool and eggs

Pediculosis Capitis

- Direct visualization of the parasite and nits
- It is possible to see if the nits are full (vital nits) or empty which helps determine the success or failure of treatment

Pediculosis Pubis

- It is possible to easily see the parasite attached to adjacent pubic hairs or hairs at other sites

Lichen Planus

- Peppering
- Brown blotches
- White reticular areas (Wickham's striae)
- Negative pigment network/reticular depigmentation is in the dermoscopic differential diagnosis of Wickham's striae

Warts

- Red and or black dots (thrombosed capillaries)
- With or without a white halo

Psoriasis

- Red scaly plaque or plaques
- Diffuse distribution of glomerular vessels identical to Bowen's disease
- Distribution of lesions will help differentiate Psoriasis from Bowen's disease
- Both can have single or multiple lesions

Nail Folds

- Normal capillary loops are hairpin shaped and run parallel to the axis of the nail
- The main value of nail fold dermoscopy is the early diagnosis of scleroderma before there are positive clinical and serologic findings

Scleroderma Pattern

- The triad of:
 - rarefied capillaries (less than 6 loops per mm)
 - thin loops, megacapillaries
 - pearly shining sclerosis "cotton balls"

Dermatomyositis

- Mega, twisted, branched loops, microhemorrhage

Lupus Erythematosus

- Considerable variation of loops, branching, twisted, microhemorrhage

Trichoscopy

- The use of dermoscopy to evaluate scalp skin and hair follicles
- Structures that can be visualized include
 - Hair shafts
 - Hair follicle openings
 - Perifollicular epidermis
 - cutaneous microvasculature
- Higher magnifications (20 to 70-fold) with digital systems and fluid (70% ethanol) are preferred
- Hand held instrumentation with lower magnification and other fluids such as emersion oil or gels can also be used

Genetic Hair Shaft Abnormalities

MONILETHRIX

- Multiple constrictions of the hair shaft alternating with elliptical nodosities that look like a “pearl necklace”
- A high tendency to fracture which gives hair a stubble like appearance
- Hair shafts bend regularly in multiple places and curve in different directions “regularly bended ribbon sign”

NETHERTON SYNDROME

- Trichorrhexis invaginata/bamboo hair/ golf tee type characterized by invagination of the distal portion of the hair shaft into its proximal portion forming a ball in cup appearance
- Diagnosis can easily be made without the need for hair sampling and microscopic examination

PILI ANNULATI

- Alternating light and dark bands are seen clinically
 - Light bands represent cavities within the cortex
 - Cavities appear as whitish areas within a darker hair shaft
 - The opposite is true with light microscopy

Acquired Hair Diseases

ANDROGENIC ALOPECIA

- Variable hair shaft diameter
- Digital systems allow the precise measurement and monitoring of hair shaft thickness
- Identify and count vellus hairs (thin hairs less than 0.03 mm in width)
- Terminal to vellus hair ratio can be calculated without skin biopsies
- Increased percentage of thin hairs
- Decreased average hair diameter
- Predominance of hair follicle units with single hairs
- Hyperkeratotic plugs
- Perifollicular pigmentation

ALOPECIA AREATA

- Regularly distributed hyperkeratotic plugs in hair follicles (yellow dots)
- Cadaverized hairs (black dots)
- Dystrophic hairs
- Micro-exclamation point hairs
- Fibrosis with white dots in long standing cases

CICATRICAL ALOPECIA

- Scarring alopecia of different etiologies looks the same with fibrosis of follicular ostia visible as white dots
- With more advanced disease the dots coalesce to form bony white areas without visible ostia

QUIZ

Questions

- Which criteria can be used to diagnose a melanocytic lesion?
 - Milia-like cysts and pigmented follicular openings
 - Arborizing vessels, ulceration and pigmentation
 - A central white patch plus fine peripheral pigment network
 - Lacunae and black homogenous blotches
 - Pigment network, brown globules, homogeneous blue color, or parallel patterns
- Diagnosing a melanocytic lesion by default means that:
 - There are high risk criteria at the periphery of the lesion that are hard to identify
 - There are criteria for a seborrheic keratosis or basal cell carcinoma associated with pigment network and brown globules
 - There is an absence of criteria to diagnose a melanocytic lesion, seborrheic keratosis, dermatofibroma, pyogenic granuloma or ink-spot lentigo, therefore the lesion should be considered melanocytic
 - There is an absence of criteria to diagnose a melanocytic lesion, seborrheic keratosis, basal cell carcinoma, dermatofibroma or hemangioma, therefore the lesion should be considered melanocytic
 - None of the above
- Which criteria can be used to diagnose a seborrheic keratosis?
 - Milky-red areas, irregular streaks, and pigmented follicular openings
 - Streaks, irregular blotches and regression
 - Fissures, ridges, sharp border demarcation, milia-like cysts, follicular openings, fat fingers and hair-pin vessels
 - Rhomboid structures and/or circle within a circle
 - Diffuse brown color, glomerular vessels and milia-like cysts
- Which criteria can be used to diagnose a basal cell carcinoma?
 - Pigment network and arborizing vessels
 - Arborizing and pinpoint vessels plus multifocal hypopigmentation
 - The absence of a pigment network, arborizing vessels, pigmentation, ulceration, spoke-wheel structures
 - Glomerular vessels, ulceration and blue ovoid nests of pigmentation
 - Islands of black blotches, arborizing vessels and moth-eaten borders

5. Vascular lesions can contain the following criteria:
 - A. Out of focus lacunae-like globules
 - B. A variable number of red, sharply demarcated vascular spaces called lacunae and fibrous septae
 - C. Ten to twenty major and minor lacunae and thromboses
 - D. A minimal of two well-developed glomerular vessels
 - E. Fibrous septae, peppering, and blue dark lacunae
6. Dermatofibromas can be associated with the following criteria:
 - A. Pigment network, arborizing vessels and central white patch
 - B. A central white patch that is never located at the periphery
 - C. A central white patch and peripheral pigment network
 - D. A complete absence of blood vessels and a few milia-like cysts
 - E. Multifocal hypopigmentation, arborizing vessels and a central bluish-white veil
7. Melanoma-specific criteria on the trunk and extremities can contain this combination of criteria:
 - A. Asymmetry of color and structure, a cobblestone global pattern and regular globules or blotches
 - B. A multicomponent global pattern, symmetry of color and structure, regular network, regular globules and regression
 - C. Polymorphous vessels, arborizing vessels, two colors and regular streaks
 - D. Irregular network, irregular globules, irregular blotches and regression
 - E. Rhomboid structures and the parallel-ridge pattern
8. Dysplastic nevi typically have the following combination of criteria:
 - A. Symmetry of color and structure and no melanoma-specific criteria
 - B. Asymmetry of color and structure, irregular network, regular blotches and regular streaks
 - C. Multifocal regression, peppering, regular pigment network, regular dots and globules
 - D. Pinpoint, arborizing and glomerular vessels plus several melanoma-specific criteria
 - E. Asymmetry of color and structure plus several melanoma-specific criteria
9. Which statement is *true* about Spitz nevi?
 - A. They can have ten different patterns
 - B. A Spitzoid lesion only refers to the starburst or pink patterns
 - C. Melanoma is not in the differential diagnosis of regular starburst pattern
 - D. In an adult, most Spitzoid lesions do not need to be excised
 - E. Symmetrical and asymmetrical starburst patterns can be seen in melanoma
10. The following statement best describes the criteria seen in superficial spreading melanomas.
 - A. Criteria associated with a benign nevus are never seen
 - B. They contain several well developed melanoma-specific criteria such as symmetry of color and structure and one prominent color
 - C. Usually they have several well developed melanoma-specific criteria such as asymmetry of color and structure, multicomponent global pattern, regular network, regular globules and regular streaks
 - D. They contain a variable number of melanoma-specific criteria such as asymmetry of color and structure, multicomponent global pattern, irregular local criteria, five or six colors and polymorphous vessels
 - E. Are usually feature poor or featureless

Answers

1. E. Criteria to diagnose a melanocytic lesion include any variation of pigment network (regular and/or irregular), multiple brown dots and/or globules, homogeneous blue color of a blue nevus and parallel patterns seen on acral skin. The default category is the last way to diagnose a melanocytic lesion. Milia-like cysts, and follicular openings can be seen in melanocytic lesions but are not primary criteria to make the diagnosis. Answers A, B and C diagnose a basal cell carcinoma, dermatofibroma and hemangioma.
2. D. Diagnosing a melanocytic lesion by default means that one does not see criteria for a melanocytic lesion, seborrheic keratosis, basal cell carcinoma, dermatofibroma or hemangeoma. Default is an absence of criteria. One has to memorize all of the criteria from each specific potential diagnosis to be able to diagnose a melanocytic lesion by default. Dermoscopy cannot be mastered by osmosis. It is essential to study and practice the technique routinely in one's daily practice. Ink-spot lentigo and pyogenic granuloma are not in this algorithm.

3. C. All of the criteria used to diagnose seborrheic keratosis are commonly seen in daily practice. Melanoma-specific criteria can also be seen in atypical seborrheic keratosis. Beware of seborrheic keratosis-like melanomas. Milky red areas, irregular streaks, regression, rhomboid structures and circle within a circle are all melanoma-specific criteria that are more sensitive and specific for melanoma but could be found in seborrheic keratosis. Glomerular vessels are a primary criterion to diagnose Bowen's disease and are not seen in seborrheic keratosis.
4. C. Basal cell carcinomas are usually a clinical diagnosis and dermoscopy is used to confirm ones clinical impression. By definition, if one sees pigment network the lesion could not be a basal cell carcinoma. A subset of melanomas can be indistinguishable from basal cell carcinoma with pigmentation and arborizing vessels. Pinpoint and glomerular vessels could be seen but they would be out shadowed by arborizing vessels. If not, one could be dealing with a basal cell-like melanoma. Moth-eaten borders are seen in lentigines and flat seborrheic keratosis, never in basal cell carcinomas.
5. B. The hallmark of vascular lesions are lacunae, vascular spaces with well-demarcated sharp borders. There is no set number of lacunae needed to make the diagnoses. At times one has to use their imagination to decide if the margins fit the criteria for vascular spaces. Different shades of red, blue and even black are typically seen. Black homogeneous color usually represents thrombosis. Major and minor lacunae do not exist. Fibrous whitish septae and/or bluishwhite color are routinely seen in typical hemangiomas. At times it is not possible to differentiate lacunae and red color of a hemangioma from the milky-red areas that can contain out-of-focus reddish globules seen in melanoma.
6. C. Dermatofibromas are ubiquitous benign tumors and in most cases dermoscopy is not needed to make the diagnosis. A central white patch and pigment network the primary criteria to make the diagnosis may or may not be present. It might not be possible to differentiate an atypical dermatofibroma from a melanoma if melanoma-specific criteria are identified. There are innumerable ways that the central white patch can appear, and in many cases it is not centrally located. Telectangietatic vessels with polymorphous shapes are commonly seen but basocell-like arborizing vessels would make the diagnosis of a dermatofibroma unlikely.
7. D. Irregularity is the name of the game if criteria are to be considered melanoma-specific. Melanoma-specific criteria can be seen in both benign and malignant pathology but are more sensitive and specific for melanoma. There is not a single melanoma-specific criterion that is pathognomonic for melanoma. One should learn their definitions and study as many classic textbook examples as possible. Rhomboid structures help diagnose melanoma on the face and the parallel-ridge pattern can be seen in acral melanomas.
8. E. Dysplastic nevi are ubiquitous in the light skinned population and can be indistinguishable clinically and dermoscopically from melanoma. They usually look more benign than malignant with dermoscopy; however, there are melanomas that do not have well developed melanoma-specific criteria. Vessels of any kind are not typically seen except in pink feature poor dysplastic nevi. They can have a variable number of melanoma-specific criteria (e.g., irregular pigment network, irregular dots and/or globules, irregular blotches) that are not as well developed as those seen in melanoma. Streaks, regression and many colors are not usually seen and should raise a "red flag" of concern that the lesion might be a melanoma.
9. E. Spitzoid lesions are always a "red flag" for concern. Even symmetrical patterns can be seen in melanoma. There are only six patterns (starburst, globular, homogeneous, pink, black network, atypical). One often has to use their imagination to diagnose a Spitzoid lesion. Since symmetrical and asymmetrical Spitzoid patterns can be found in melanoma, they should all be excised in children as well as in adults. A dermatopathologist that specializes in melanocytic lesions is good, while one that has expertise in Spitzoid lesions is ideal. Even experienced dermatopathologists have trouble differentiating atypical Spitzoid lesions from melanoma, and atypical Spitzoid lesions have the potential to metastasize to regional lymph nodes.
10. D. Superficial spreading melanoma can have it all as far as the spectrum of melanoma-specific criteria goes. The criteria can be well developed or difficult to identify. Criteria associated with benign melanocytic lesions can also be seen. The more high risk criteria identified in the lesion, the greater the chance that one is dealing with a melanoma. Nodular and amelanotic melanoma are more likely to be feature poor or featureless.

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RADIOLOGIC FINDINGS

MINSUE CHEN

MELISSA A. BOGLE

ASRA ALI

Radiologic findings of various cutaneous disorders are organized and presented as follows (Table 32-1):

- Bullous
- Connective tissue
- Cornification
- Hair and nails
- Hematologic
- Infectious
- Infectious, fungal
- Inflammatory
- Malignant potential
- Metabolic
- Pigmentation
- Vascular
- Other

TABLE 32-1 Radiological Findings in Skin Diseases and Related Conditions

Disease	Etiology	Clinical Features	Radiologic Findings
Bullous			
Junctional epidermolysis bullosa (Herlitz/Letalis)	Autosomal recessive Defect in $\alpha 6\beta 4$ -integrin	Generalized bullae, perioral granulation tissue, absent/shed nails, dysplastic teeth, respiratory edema	Pyloric atresia
Connective Tissue			
Bushke-Ollendorf (connective tissue nevus syndrome)	Autosomal dominant	Dermatofibrosis lenticularis disseminata, juvenile elastomas	Asymptomatic oval opacities on x-ray (osteopoikilosis) may be mistaken for bone metastases
Ehlers-Danlos syndrome	Autosomal dominant Autosomal recessive (kyphoscoliosis type VI; dermatosparaxis type VIIC) Collagen and proteins involved in collagen production	Skin hyperextensibility, cigarette paper texture to scars, hypermobile joints; congenital dislocation of the hip (types I, IV, VIIA and VIIB)	Mitral valve prolapse and aortic root dilatation; wide joint spaces
Goltz syndrome (focal ectodermal dysplasia)	X-linked dominant	Fat herniation, cutaneous papillomas	Osteopathia striata (linear vertical opacities in metaphyses of the bones); lobster claw deformity of the hand
Lipoid proteinosis (hyalinosis cutis et mucosae, Urbach-Wiethe disease)	Autosomal recessive Defect of ECM gene	Hoarse cry at birth; early bullae with later pearly papules on face, eyelid, neck, mucosa, and extremities; alopecia, parotiditis, large wooden tongue, abnormal teeth, seizures	“Bean bag” hippocampal calcifications in the temporal lobe; deposits may also be found in the vocal cords and other laryngeal structures.
Marfan syndrome	Autosomal dominant Defect of fibrillin-1		Kyphoscoliosis; pectus excavatum (depression of sternum), pectus carinatum (projection of sternum); mitral valve prolapse and aortic root dilation
Pseudoxanthoma elasticum	Autosomal recessive Autosomal dominant Defect in ABCC6 gene	Yellow pebbling of skin	Mitral valve insufficiency, artery calcification, coronary artery disease, peripheral vascular disease; gastric or duodenal hemorrhage

Continued

TABLE 32-1 (Continued)

Disease	Etiology	Clinical Features	Radiologic Findings
Cornification			
Chondrodysplasia punctata (Conradi-Hunermann-Happle syndrome)	X-linked dominant Defect in emopamil binding protein (EBP) (AKA 3beta-hydroxysteroid-Δ8-Δ7-isomerase)	Ichthyosiform erythroderma in Blaschko's lines, patchy alopecia, asymmetric focal cataracts	Stippled epiphyses (chondrodysplasia punctata), unilateral limb shortening, scoliosis
Congenital hemidsyplasia with ichthyosiform and limb defects (CHILD)	X-linked dominant Defect in NSDHL gene encoding 3beta-hydroxysteroid-dehydrogenase	Unilateral ichthyosiform erythroderma	Ipsilateral hypoplasia of limbs, bones, organs
Epidermal nevus syndrome (Ichthyosis hystrix)	Unknown	Epidermal nevi; tumors of fibrous and vascular tissue; seizures	Skeletal abnormalities associated with location of nevi; cerebral angiomas; systemic malignancies
Palmoplantar keratoderma with periodontosis (Papillon-Lefèvre syndrome)	Autosomal recessive Defect in cathepsin C	Palmoplantar keratoderma, psoriasiform hyperkeratotic plaques on elbows and knees, periodontitis, gingivitis	Calcification of dura mater, exfoliation of teeth
Hair and Nails			
Hypohidrotic ectodermal dysplasia (Christ-Siemens-Touraine syndrome)	X-linked recessive (extodysplasin gene) Autosomal dominant (NEMO)	Smooth, dry skin; hypo/anhidrosis with concomitant pyrexia	Jaw radiographs: hypodontia or dental abnormalities (peg shaped teeth)
Menkes syndrome (occipital horn syndrome)	X-linked recessive Defect of ATP7A gene	Pili torti, doughy skin; occipital horns develop from ectopic bone formation with in the aponeuroses of the posterior neck muscles	Elongated and tortuous vessels, subdural hematomas, tumors and cysts of the epidermis and epidermal appendages, occipital horns (exostoses); delayed myelination of white matter.
Nail patella syndrome	Autosomal dominant Defect in LMX1B gene	Dysplastic nails (triangular lunula), nephropathy (may be subclinical), Lester iris	Hypoplastic or absent patellae; posterior iliac horns (Fong's syndrome when isolated finding)
Hematologic			
DiGeorge syndrome	Sporadic zinc finger anomaly TBX1 gene	Congenital absence of thymus and parathyroid; abnormal aorta, hypocalcemia, tetany; recurrent fungal and viral infections, cardiac problems most common cause of death	Absent thymic shadow

Continued

TABLE 32-1 (Continued)

Disease	Etiology	Clinical Features	Radiologic Findings
Fanconi's syndrome (familial pancytopenia)	Autosomal recessive Mutation in 1 of the Fanconi anemia complementation group genes (FANC)	Pigment abnormalities, severe anemia, thrombocytopenia, hyperreflexia, retinal hemorrhage, testicular hypoplasia	Aplasia of the radius, absent thumbs
Infectious			
Congenital syphilis, early	<i>Treponema pallidum</i>	Clinical manifestations exhibit at birth or shortly thereafter	Epiphysitis of long bones (pain on motion, Parrot pseudoparalysis), osteochondritis, sawtooth lesion on x-ray in the metaphysic, onion-peel periosteum sign (multiple layers of new bone)
Congenital syphilis, late	<i>Treponema pallidum</i>	Late skeletal findings usually manifest in the latter half of the first decade or in the second decade	Knee perisynovitis (Clutton joints), bulldog jaw: mandibular protuberance, gummas (skull, long bones), saber shins: anterior bowing of tibia, Higoumenaki sign (unilateral hyperostosis of the medial clavicle), scaphoid scapulae: concavity of vertebral border of scapulae
Infectious, Fungal			
Aspergillosis	<i>Aspergillus</i> species	Disseminated disease seen in immunocompromised patients; saprophytic colonization in immunocompetent hosts	Aspergilloma (pulmonary cavitary lesions), alveolar infiltrates
Blastomycosis	<i>Blastomyces dermatitidis</i>	Atypical pulmonary disease with skin and bone involvement	Alveolar infiltrates (reticulonodular pattern), pleural effusion, similar to that of tuberculosis
Coccidioidomycosis	<i>Coccidioides immitis</i>	Desert rheumatism, arthralgia; erythema multiforme or erythema nodosum may occur	Infiltrates, nodules, cavity, mediastinal or hilar adenopathy, pleural effusion
Cryptococcosis	<i>Cryptococcus neoformans</i>	Found in avian excreta and soil, may coexist with sarcoid	Patchy pneumonitis, granulomas; may also be found in the bones and urologic organs
Histoplasmosis	<i>Histoplasma capsulatum</i> <i>Histoplasma capsulatum</i> var. <i>duboisii</i>	Oral disease, Addison disease from adrenal infiltration	Patchy pulmonary infiltrates, upper lobe cavitations, healed lesions that appear as residual pulmonary nodules, lesions simulate that of tuberculosis; adrenal calcification

Continued

TABLE 32-1 (Continued)

Disease	Etiology	Clinical Features	Radiologic Findings
Mucormycosis	<i>Rhizomycor absidia</i> <i>Rhizomycor rhizopus</i>	Patients are oftentimes immunocompromised (organ transplantation, diabetic)	Sinus disease, bone erosion
Mycetoma (Madura foot)	Fungal or bacterial infection of the subcutaneous tissue	Characteristically on the foot, follows implantation with draining sinus and gross deformity	Honeycomb bone destruction in the foot, extension to underlying bone and joints leads to osteomyelitis and arthritis
Nocardiosis	<i>Nocardia asteroides</i>	Opportunistic infection	Pulmonary lesion simulates tuberculosis
Paracoccidioidomycosis	<i>Paracoccidioides brasiliensis</i>	Most common in Latin American countries, poor hygiene, malnutrition	Confluent nodular infiltrates in the lung; adrenal lesions
Inflammatory			
Dermatomyositis (Fig. 32-1)	Unknown	Cutaneous findings with proximal muscle weakness, Gottron's papules, heliotrope rash, periungual telangiectasias	Osteoporosis, calcinosis; interstitial pneumonia
Kawasaki's syndrome (mucocutaneous lymph node syndrome)	Unknown	Mostly commonly in Japan; 5 of 6 criteria need to be met for diagnosis (fever unresponsive to antibiotics, conjunctivitis, erythema/edemas of palms, oral lesions, polymorphous eruption, cervical lymphadenopathy)	Echocardiogram—coronary artery aneurysm; coronary artery calcifications
Morphea	Unknown	Localized scleroderma	Melorheostosis (dense linear pattern of hyperostosis) resembling candle wax flowing
Reiter's syndrome	Unknown	Develops after enteric infections (reactive arthritis); seronegative spondyloarthritides; sacroiliitis, spondyloarthritis	Enthesopathy, bone lucency, new bone formation; feet are involved with relative sparing of hands
SAPHO syndrome	Unknown	Eponym for the combination of synovitis, acne, pustulosis, hyperostosis, and osteitis	Hyperostosis, osteitis, "bullhead" sign in sterno-costoclavicular region on bone scan (sternoclavicular hyperostosis); may be indistinguishable from chronic osteomyelitis, hypervitaminosis A, retinoid use

Continued

TABLE 32-1 (Continued)

Disease	Etiology	Clinical Features	Radiologic Findings
Sarcoidosis	Unknown	Granulomatous multisystem disorder	Bilateral hilar adenopathy, interstitial pulmonary infiltrates, osteolytic lesions; splenomegaly, renal and bone involvement may be seen, as well as neurosarcoid
Malignant Potential			
Cockayne syndrome	Autosomal recessive Defect in DNA helicase	“Cachectic dwarf”: long limbs, contractures, cool acral extremities, photosensitivity, progressive neural degeneration, deafness, retinitis pigmentosa, cataract, dental caries	Intracranial calcifications (Fig. 32-2)
Cowden disease	Autosomal dominant Defect in PTEN gene	Tricholemmomas, oral papillomas	Mammogram to identify breast lesions; barium swallow, upper and lower GI endoscopy for hamartomatous polyps; ovarian cysts; goiter
Dyskeratosis congenita	X-linked recessive Defect in dyskerin gene	Reticulated pigmentation of skin, dystrophic nails, premalignant oral leukoplakia	Pulmonary fibrosis
Gardner’s syndrome	Autosomal dominant Defect in APC gene (β -catenin)	Epidermoid cysts, fibroma, desmoids tumor	Osteomas; odontomas/supernumerary teeth, hyperostosis, thyroid tumors, intestinal adenomatous polyps
Gorlin-Goltz (basal cell nevus syndrome) (See also Chap. 23)	Autosomal dominant Defect in PATCHED gene	Basal cell carcinomas, palmoplantar pits, frontal bossing, medulloblastoma, ovarian fibromas, fibrosarcoma; Albright’s sign: short fourth metacarpal (Figure 32-3)	Odontogenic jaw cysts, calcification of falx cerebri (Fig. 32-4), rib deformities, bifid ribs, kyphoscoliosis, long bone cysts
Peutz-Jeghers syndrome	Autosomal dominant Defect of STK11 gene	Periorificial mucocutaneous melanocytic macules (lentigenes)	Intestinal hamartomatous polyps most numerous in the jejunum and ileum
Metabolic			
Alkaptonuria	Autosomal recessive Deficiency of homogentisic acid oxidase	Blue-black discoloration of sclera and cartilage, dark sweat/urine/cerumen, arthropathy (large joints); deafness	Aortic and intervertebral disk calcification (Fig. 32-5); renal stones, prostate concretions; spinal x-rays are diagnostic.

Continued

TABLE 32-1 (Continued)

Disease	Etiology	Clinical Features	Radiologic Findings
Calcinosis cutis	Calcium deposition without bone formation	Three main types: dystrophic (damaged tissue with normal calcium/phosphorus levels); metastatic (normal tissue with abnormal calcium and phosphorous levels); idiopathic (no tissue damage or metabolic disorder)	Visceral and nonvisceral calcification; depends on type of cutaneous calcinosis
Gaucher disease	Autosomal recessive Deficiency in glucocerebrosidase	Type I: manifests in adults as hyperpigmentation, hepatosplenomegaly, lymphadenopathy, pancytopenia. Type II: manifests in infancy as hepatosplenomegaly, rapid neurologic deterioration, chronic aspiration, pneumonia. Bone marrow: Gaucher cells (“crumpled tissue paper”)	Splenomegaly, osteoprosis from infiltration by Gaucher cells, bone infarcts, avascular necrosis of femoral head, Erlenmeyer flask deformity of long bones, periosteal new bone formation
Gout	Deposition of monosodium urate	Tophi on helix of ears, elbows, fingers and toes	Soft tissue tophi may calcify; punched out cystic lesions on articular surfaces without osteoporosis.
Hepatolenticular degeneration (Wilson disease)	Autosomal recessive Defect of ATB7B gene	Liver failure	On MRI, changes in the putamen and caudate nuclei may be found from copper deposition; osteoporosis and “fringed” appearance of articular surfaces; cirrhosis
Pigmentation			
Albright’s hereditary osteodystrophy (McCune-Albright syndrome)	Postzygotic mutation Defect in GNAS1 gene encoding alpha subunit of the G stimulatory protein that regulates adenylate cyclase	“Coast of Maine” café-au-lait macules, precocious puberty, endocrine abnormalities (hyperthyroidism); dimpling over the metacarpophalangeal joints (Albright sign)	Polyostotic fibrous dysplasia, recurrent fractures, bowing of the limbs, limb-length discrepancies, bone cysts, sclerosis at the skull base; findings often seen associated with area of pigmentation
Hypomelanosis of Ito (incontinentia pigmenti achromians)	Unknown	Marbled cake hypopigmentation in Blaschko’s lines, seizures	Musculoskeletal abnormalities asymmetry

Continued

TABLE 32-1 (Continued)

Disease	Etiology	Clinical Features	Radiologic Findings
Incontinentia pigmenti (Bloch-Sulzberger syndrome)	X-linked dominant Defect on NEMO gene	Linear arrangement of lesions, appearance depends on stage of development (vesicular, verrucous, hyperpigmentation, hypopigmentation)	Peg or conical shaped teeth; brain atrophy
Neurofibromatosis I	Autosomal dominant Defect in neurofibromin	Diagnose optic glioma with MRI, occurs during the first 4 years of life; bilateral in 4%. It is the most common intracranial tumor associated with neurofibromatosis type 1	Sphenoid wing dysplasia, cortical thinning of long bones, bowing of the tibia (Fig. 32-6), tibial pseudoarthrosis, scoliosis, optic glioma
Neurofibromatosis II	Autosomal dominant Defect in merlin	Café-au-lait with hair	Acoustic neuromas, cranial nerve schwannomas, brain tumors
Tuberous sclerosis	Autosomal dominant Defect in hamartin (ch 9) or tuberlin (ch 16)	Ash-leaf hypo-pigmented patches, connective tissue tumors	Hamartomas at multiple sites. Phalangeal cysts, periosteal thickening, paraventricular calcifications, cortical tubers, subependymal hamartomas; angiomyolipoma, pulmonary lymphangiomatosis, cardiac rhabdomyoma
Vascular			
Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)	Autosomal dominant Defect in endoglin gene or ALK1 gene	Telangiectasias, epistaxis	CT scan: pulmonary arteriovenous malformations, liver, kidney, and splenic lesions
Proteus syndrome	PTEN	Symmetrical overgrowth; capillary malformations and subcutaneous masses	Bony overgrowth of the cranium of facial structures, soft tissue and bony hypertrophy
Ataxia-teleangiectasia (Louis-Bar syndrome)	ATM gene	Telangiectasias, café-au-lait macules	Sinopulmonary infections, thymus maldevelopment, subnormal bone age
Blue rubber nevus syndrome (Bean syndrome)	Unknown	Venous malformations	GI venous malformation with endoscopy
Klippel-Trenaunay-Weber	Unknown	Capillary malformation, usually on lower extremity. Parkes-Weber variant: arterioventricular fistulas, high-output heart failure	Underlying bone and soft tissue hypertrophy, varicosities, thromboses, destructive bone lesions, limb hypertrophy and abnormalities, compensatory scoliosis

Continued

TABLE 32-1 (Continued)

Disease	Etiology	Clinical Features	Radiologic Findings
Maffucci syndrome (enchondromatosis with hemangioma)	Unknown	Grapelike superficial and deep venous malformations (rarely malignant). Between 15% and 30% of enchondromas transform to chondrosarcoma	Multiple enchondromas (phalanges, long bones), fractures, bowing, limb length discrepancies; phleboliths in hemangiomas; Ollier disease: multiple enchondromas without hemangiomas
Sturge-Weber (encephalotrigeminal angiomatosis)	Unknown	Facial capillary malformation, seizures, hemiparesis, choroidal malformations, glaucoma	Tram track (double contour) calcifications of cerebral cortex, leptomeningeal angiomatosis; underlying soft tissue and skeletal hypertrophy
Other			
Dermoid cyst	Sequestration of skin along embryonic closure lines.	Present at birth on the head and neck most commonly	MRI to diagnose intracranial or intramedullary cysts
Langerhans' cell histiocytosis	Unknown	Crusted purpuric papules and a scaly seborrheic-like eruption in the scalp and groin	Letterer-Siwe: honeycomb lung involvement with cystic cavities (Fig. 32-7); floating teeth, osteolytic bone lesions. Hand-Schüller-Christian: "punched out" osteolytic skull lesions (Fig. 32-8); eosinophilic granulomas: granulomatous bone lesion (Fig. 32-9)
Multicentric reticulohistiocytosis	Unknown	Destructive polyarthritis	Resorption of subchondral bone, arthritis mutilans, accordion hand (shortening of fingers and mutilation)

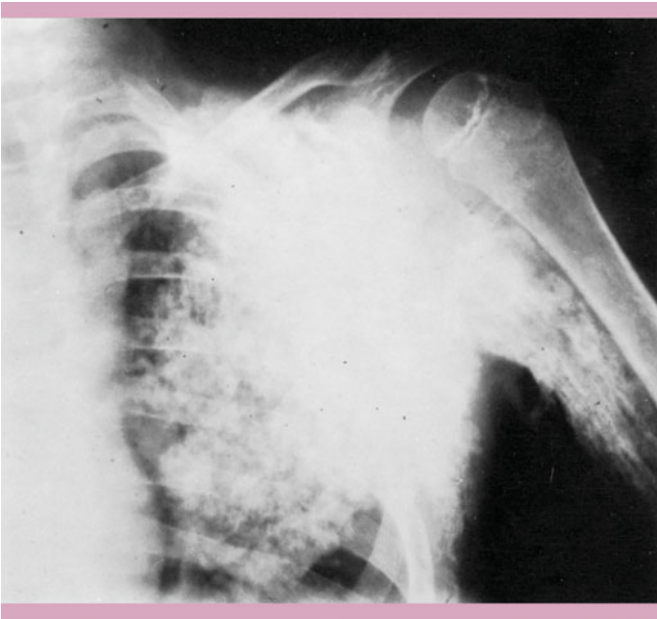


FIGURE 32-1 Dermatomyositis. (Reprinted with permission from Freedberg IM et al: Fitzpatrick's Dermatology in General Medicine, 6th ed. New York: McGraw-Hill; 2003.)

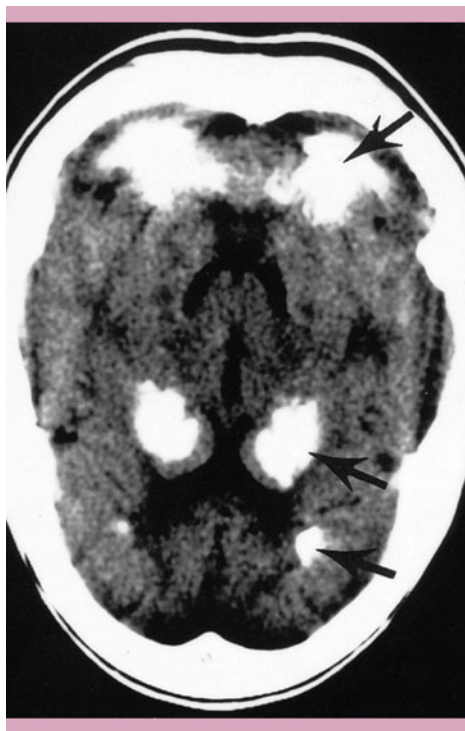


FIGURE 32-2 Intracranial calcifications of Cockayne syndrome. (Reprinted with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th ed. New York: McGraw-Hill; 2003.)



FIGURE 32-3 Albright's sign of basal cell nevus syndrome. (Reprinted with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th ed. New York: McGraw-Hill; 2003.)

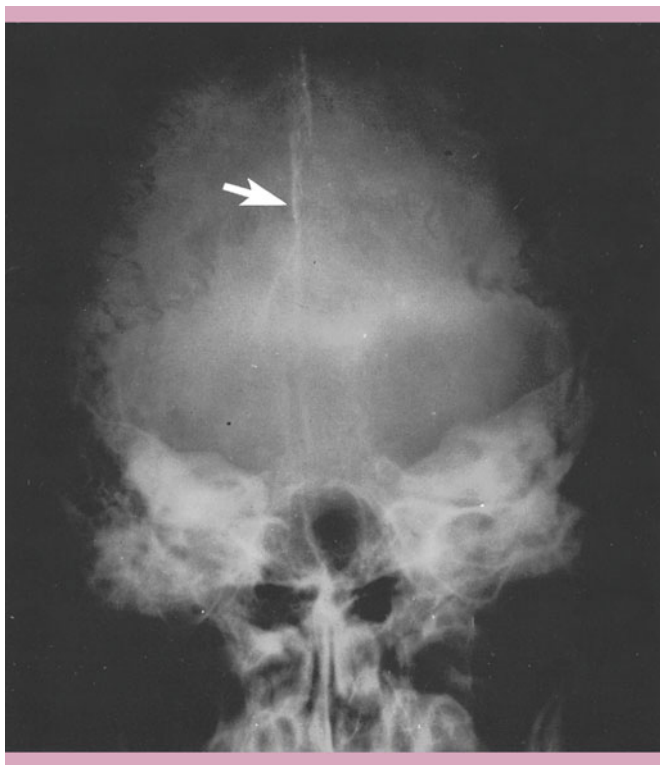


FIGURE 32-4 Calcification of falx cerebri in basal cell nevus syndrome. (Reprinted with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th ed. New York: McGraw-Hill; 2003.)

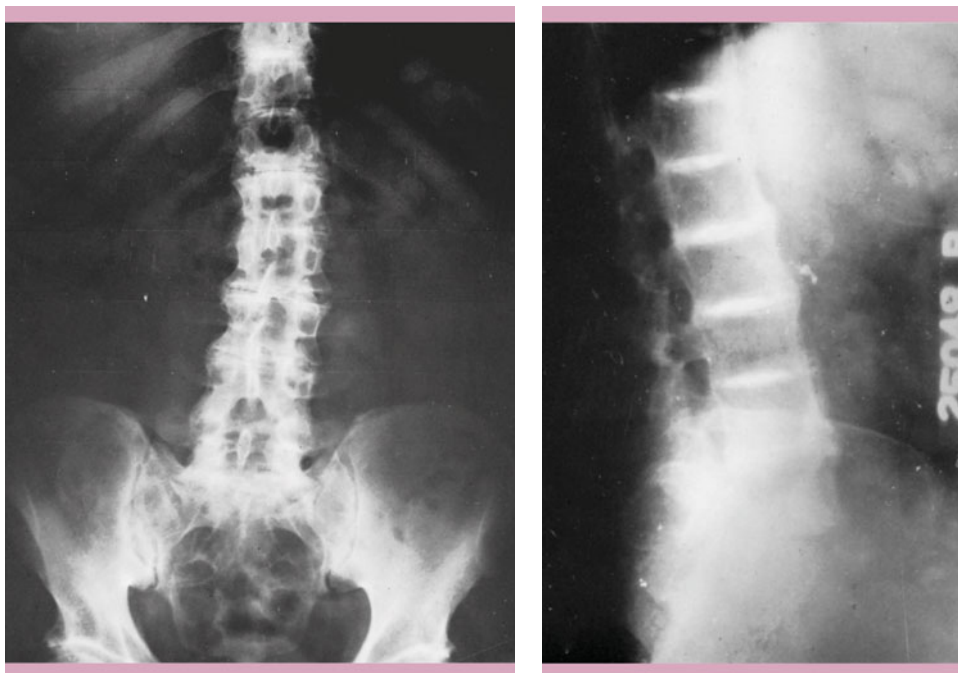


FIGURE 32-5 Radiologic findings in an alkaptonuric patient showing aortic and vertebral disk calcification. (Reprinted with permission from Wolff, et al., *Fitzpatrick's Dermatology in Internal Medicine*, 7th edition, McGraw-Hill; 2008.)



FIGURE 32-6 Tibial bowing seen in neurofibromatosis. (Reprinted with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th ed. New York: McGraw-Hill; 2003.)

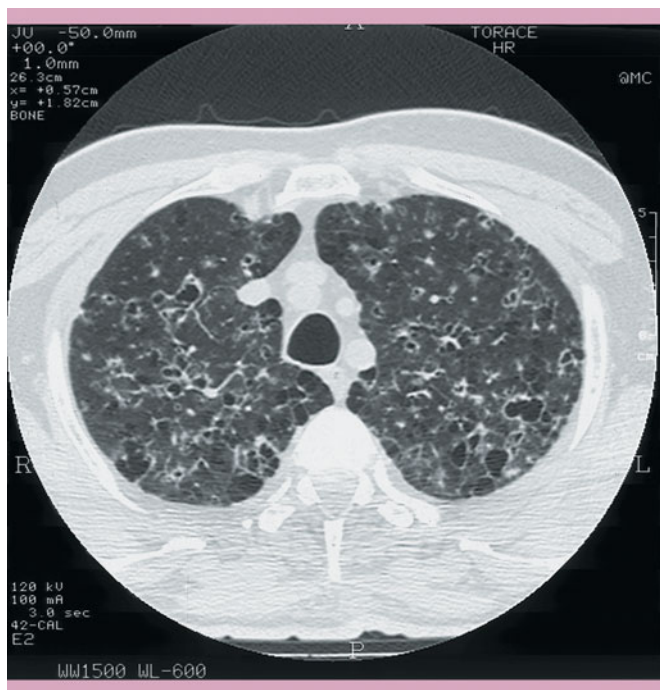


FIGURE 32-7 Letterer-Siwe disease, “honeycomb lung”. (Reprinted with permission from Wolff, et al., *Fitzpatrick’s Dermatology in Internal Medicine*, 7th edition, McGraw-Hill; 2008.)

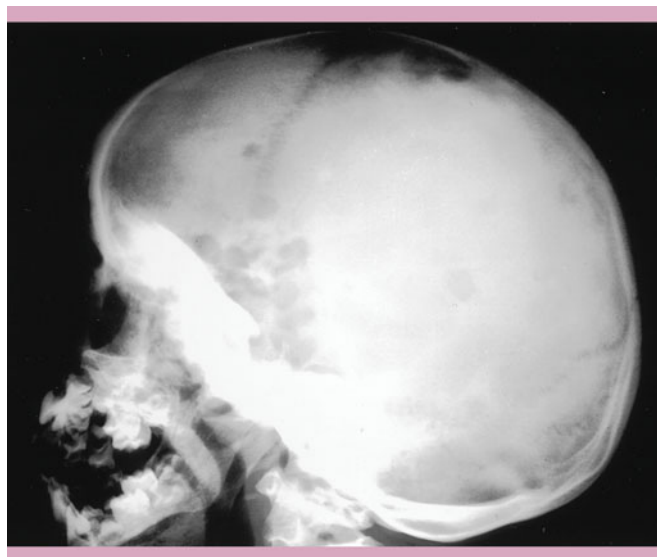


FIGURE 32-8 Hand-Schüller-Christian disease, osteolytic skull lesions. (Reprinted with permission from Wolff, et al., *Fitzpatrick’s Dermatology in Internal Medicine*, 7th edition, McGraw-Hill; 2008.)



FIGURE 32-9 Eosinophilic granulomas. (Reprinted with permission from Wolff, et al., *Fitzpatrick’s Dermatology in Internal Medicine*, 7th edition, McGraw-Hill; 2008.)

QUIZ

Questions

Use the following answer choices for the following set of questions:

- A. Pyloric atresia
 - B. Osteopoikilosis
 - C. Osteopathia striata
 - D. Stippled epiphyses
 - E. Absent patella and posterior iliac horns
 - F. Absent thymic shadow
 - G. Aplasia of radius
 - H. Coronary artery aneurysm and coronary artery calcifications
 - I. Odontogenic jaw cysts and calcification of falx cerebri
 - J. Intervertebral disk calcification
 - K. Erlenmeyer flask deformity of long bones
 - L. Polyostotic fibrous dysplasia
 - M. Sphenoid wing dysplasia
 - N. Angiomyolipoma and rhabdomyoma
 - O. Enchondromas
 - P. Tram track calcification of cerebral cortex
 - Q. Arthritis mutilans and accordion hand
 - R. Bean bag hippocampal calcification
1. Which description matches the radiologic findings for a patient with fat herniations, cutaneous papillomas, and lobster claw deformity of the hand?
 2. Which description matches the radiologic findings for a condition with defect in neurofibromin?
 3. Which description matches the radiologic findings for a patient with a vascular malformation of the face and glaucoma?
 4. Which description matches the radiologic findings for a patient with grapelike superficial and deep venous malformations of the hands?
 5. Which description matches the radiologic findings for a patient with multicentric reticulohistiocytosis?
 6. Which description matches the radiologic findings for a condition with a defect in $\alpha 6\beta 4$ -integrin?
 7. Which description matches the radiologic findings for a patient with tetany from hypocalcemia?
 8. Which description matches the radiologic findings for a patient with fever unresponsive to antibiotics, conjunctivitis, erythema/edema of palms, oral lesions, and polymorphous eruption?
 9. Which description matches the radiologic findings for a patient with Lester irises?
 10. Which description matches the radiologic findings for a condition caused by a defect in PTCH gene?

Answers

1. C. Osteopathia striata. The condition is Goltz syndrome, characterized by fat herniations, cutaneous papillomas, and lobster claw deformity of the hand. In contrast, osteopoikilosis and stippled epiphyses are seen in Bushke-Ollendorf and Conradi-Hunermann-Happle syndromes, respectively.
2. M. Sphenoid wing dysplasia. The condition is neurofibromatosis, type I, characterized by neurofibromas, café-au-lait spots and optic gliomas. Neurofibromatosis type II is caused by a defect in merlin. Angiomyolipomas and rhabdomyomas are found in tuberous sclerosis, defects in hamartin and tuberlin.
3. P. Tram track calcification of cerebral cortex. The condition is Sturge-Weber syndrome, characterized by facial capillary malformation, seizures, hemiparesis, choroidal malformations, and glaucoma. Radiologic findings include tram track calcification of cerebral cortex. In contrast, bean bag hippocampal calcification is found in lipid proteinosis. When calcification is found on intervertebral disks, this is characteristic for alkaptonuria.
4. O. Enchondromas. The condition is Maffucci, characterized by enchondromas. Ollier disease, in contrast, is the presence of multiple enchondromas without hemangiomas.
5. Q. Arthritis mutilans and accordion hand. The condition is multicentric reticulohistiocytosis, characterized by destructive polyarthritis that may progress to arthritis mutilans and accordion hand.
6. A. Pyloric atresia. The condition is junctional epidermolysis bullosa, characterized by generalized bullae, perioral granulation tissue, absent/shed nails, dysplastic teeth, and respiratory edema.
7. F. Absent thymic shadow. The condition is DiGeorge syndrome, characterized by congenital absence of thymus and parathyroid, hypocalcemia, tetany, recurrent fungal and viral infections, and cardiac problems.
8. H. Coronary artery aneurysm and coronary artery calcifications. The condition is Kawasaki syndrome (mucocutaneous lymph node syndrome), characterized by coronary artery aneurysms on echocardiogram. Coronary artery calcifications may also be seen.
9. E. Absent patella and posterior iliac horns. The condition is nail patella syndrome, characterized by hypoplastic or absent patellae and posterior iliac horns. When posterior iliac horns are present without other abnormalities, this is called Fong syndrome.
10. I. Odontogenic jaw cysts and calcification of falx cerebri. Basal cell nevus syndrome is characterized

by defects in the PTCH gene. McCune-Albright is associated with postzygotic mutation in GNAS1 gene encoding alpha subunit of the G stimulatory protein that regulates adenylate cyclase. Deficiency in glucocerebrosidase is associated with Gaucher disease. Mutation in one of the Fanconi anemia complementation group genes (FANC) is seen in Fanconi disease.

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ELECTRON MICROSCOPY

MINSUE CHEN
ASRA ALI

INDICATIONS FOR ELECTRON MICROSCOPY

Ancillary to standard techniques (i.e., light microscopy) to resolve diagnostic difficulties in human histopathology through examination of ultrastructural findings at the cellular and organelle level

- Unclassifiable, undifferentiated neoplasms
- Supporting a diagnosis from a list of differential diagnosis
- Supporting a light microscopic diagnosis
- Determination of the primary site in metastatic neoplasms
- Medical disease of kidney
- Metabolic storage diseases
- Other congenital disorders
- Infectious agents
- Autoimmune diseases
- Certain cutaneous diseases
- Identification of foreign material in tissues

TECHNIQUE AND TISSUE PREPARATION

- Tissue preparation is similar to conventional wax embedding light microscopy: aldehyde fixation, dehydration, embedding, sectioning and examination of sections exposed to some form of radiation
- Electron microscopy differences include:
 - Image is formed by the scattering of electrons by heavy metal atoms (introduced as solutions of uranyl acetate and osmium tetroxide or lead citrate) selectively adherent to tissue sections
 - Tissue is embedded in epoxy, allowing for sectioning to a thickness of 100 nm
 - Tissue should be submitted in appropriate media (i.e., 2.5% glutaraldehyde; Karnovsky's [universal] solution)

- Fixation with glutaraldehyde provides the best structural preservation; unlike formaldehyde, glutaraldehyde is slowly penetrating. Therefore, only very small pieces of tissue are processed (i.e. 0.5 to 1 mm³ or 2–3 mm² and thickness of about 0.5 mm)
- Although processing and staining are labor intensive, turn around time can be as short as 24 to 48 hours
- Electron microscopy may also be performed on formalin fixed material from deparaffinizing a wax block. Preservation may be sufficient for diagnostic purposes although results may be variable

DIAGNOSTIC CELLS AND ORGANELLES

Langerhans Cell (Fig. 33-1)

- Bone marrow-derived
- Antigen-processing and -presenting cells
- Indented nucleus with ropey nucleolus
- Rod- and racket-shaped (terminal expansion) cytoplasmic granules (Birbeck granules) with central dotted line
- Often seen at the cell surface when membrane-bound antigen is internalized by endocytosis
- Cytoplasm contains dispersed vimentin intermediate filaments

Merkel Cell (Fig. 33-2)

- Slowly adapting type I mechanoreceptors located in sites of high tactile sensitivity
- Present among basal keratinocytes
- Nucleus is lobulated
- Cytoplasm is electron-lucent with prominent Golgi
- Margins of cells project cytoplasmic spines toward keratinocytes
- Typical granules (80 to 200 nm) have a dense core, halo, and a slightly ruffled membrane

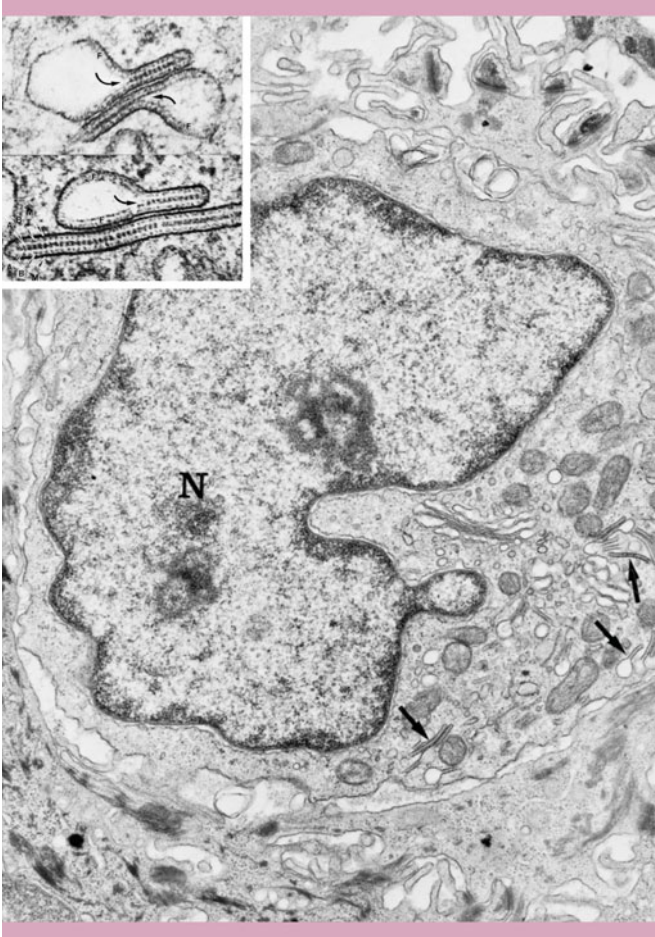


FIGURE 33-1 Langerhans cell. (Reprinted with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003.)

- Granules contain neurotransmitter-like substances
- Intermediate filaments are numerous and assume a parallel or whorled arrangement near the nucleus (dotlike pattern)

Lamellar Granules (Fig. 33-3)

- In the intercellular space and cytoplasm of the granular cell
- 0.2 to 0.3 μm in diameter
- Membrane-bound secretory organelles containing a series of alternating thick and thin lamellae (folded sheets/disk-like/liposome-like structures)
- Contain glycoproteins, glycolipids, phospholipids, free sterols, acid hydrolases, and glucosylceramides

Dermal-Epidermal Junction (Fig. 33-4)

- Interface between epidermis and dermis
- LL = lamina lucida
- LD = lamina densa
- AFib = anchoring fibrils

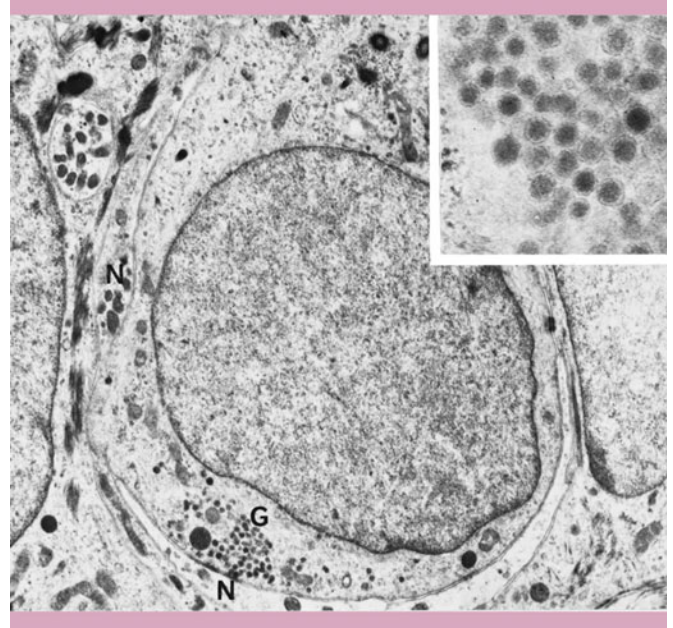


FIGURE 33-2 Merkel cell. (Reprinted with permission from Wolff et al., *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

- AFil = anchoring filaments
- HD = hemidesmosome
- KF = keratin filaments

Desmosome (Fig. 33-5)

- Calcium-dependent cell surface structures that function to promote adhesion of epidermal cells and aid in resistance to mechanical stresses
- Regularly organized submembrane plaque associated with intermediate filaments (see below)
- Intermediate line in the intercellular space
- Components of desmosome
- Desmosomal plaque
- Transmembrane glycoproteins (part of cadherin family)
- Desmosomal core

Intermediate Filaments [Fig. 33-4 (Upper Left Corner): Dense Bundle of Tonofibrils]

- About 8 to 12 nm thick
- There are five main classes (cytokeratin, vimentin, desmin, neurofilament, and glial filament)
- Only cytokeratin filaments have a distinctive ultrastructure: bundle together to form tonofilaments or tonofibrils
- Other intermediate filaments are generally non-bundling
- Fibrin may closely resemble tonofibrils, appearing as masses of short fibers that on higher magnification demonstrate periodicity

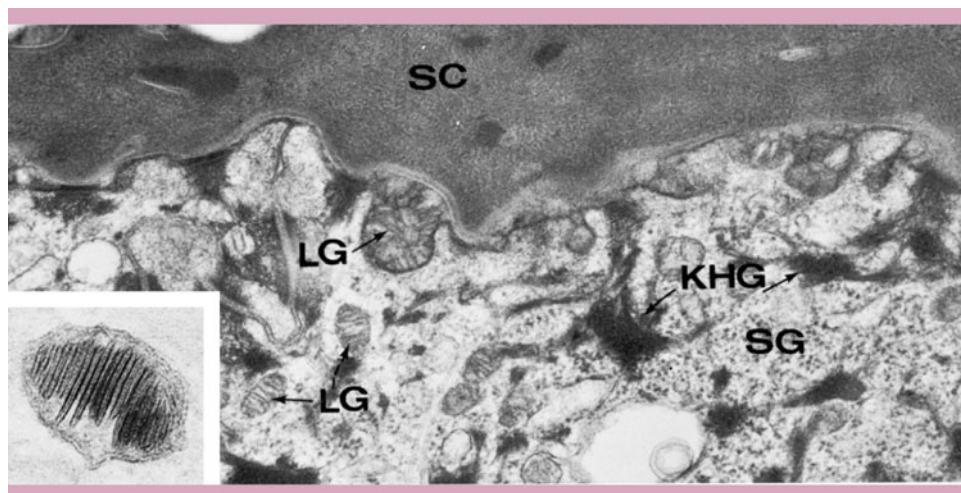


FIGURE 33-3 Lamellar granules. (Reprinted with permission from Wolff et al., *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

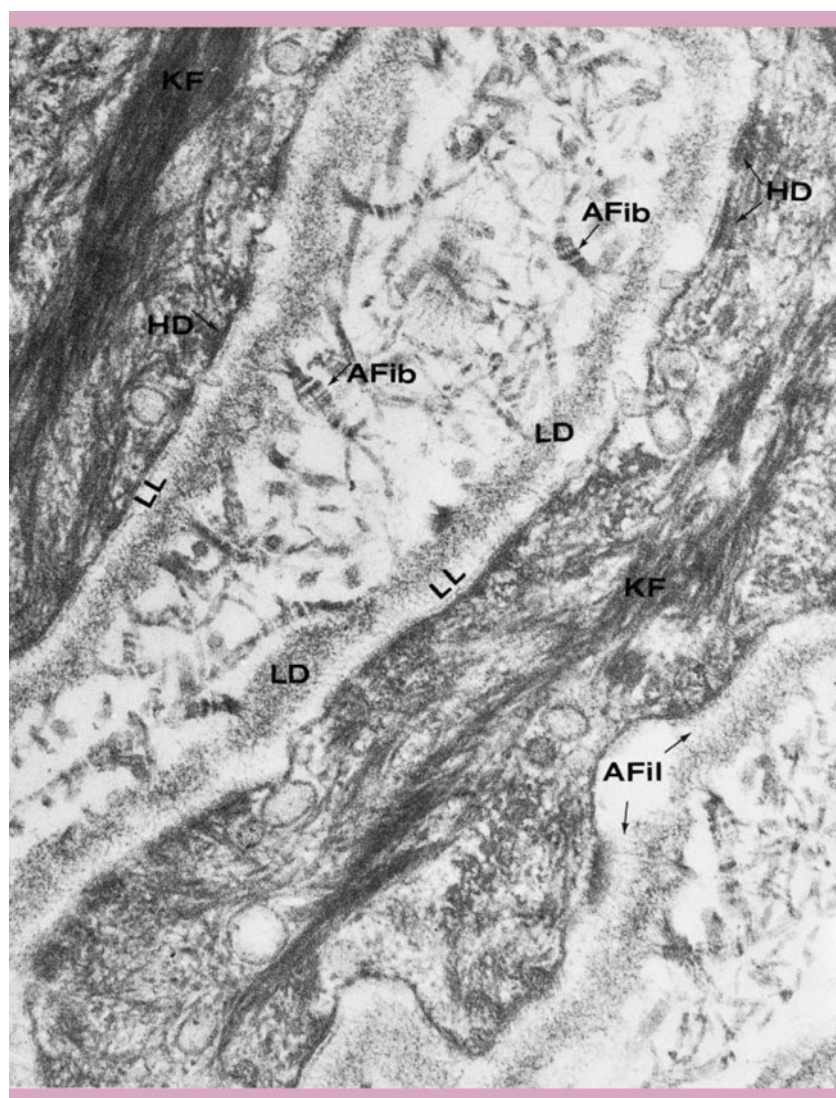


FIGURE 33-4 Dermal-epidermal junction. (Reprinted with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003.)

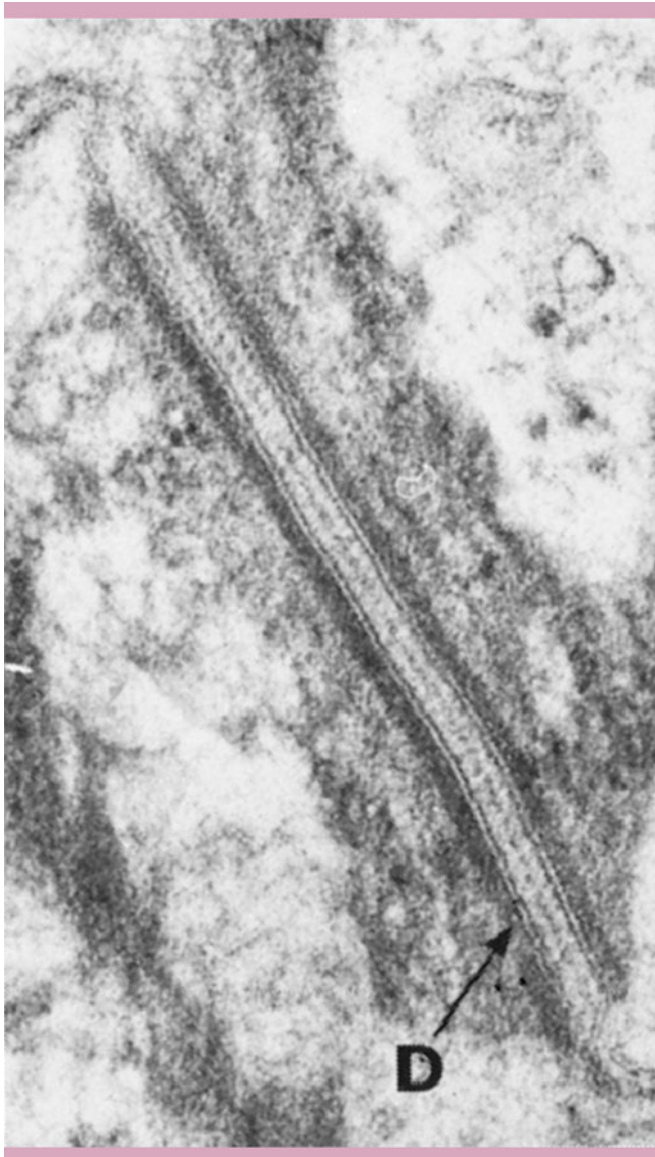


FIGURE 33-5 Desmosome. (Reprinted with permission from Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003.)

Melanocyte (Fig. 33-6)

- Contains melanosomes in cytoplasm
- Single limiting membrane
- An aggregate of melanosomes confined within a single membrane is a compound melanosome
- Melanocytes project dendrites to adjacent keratinocytes which uptake melanosomes
- Melanocytes can be distinguished from keratinocytes by the absence of keratin filaments
- Melanosomes become elongated and form ordered cross striated lattice in stage II of development
- Melanin does not appear until stage III

- Stage IV melanosomes are enriched with electron dense melanin; the lattice is obscured

Macrophage (Fig. 33-7)

- Part of the mononuclear phagocytic system
- Derived from precursor cells of bone marrow that differentiate into monocytes in the blood
- Skin macrophages express CD11c, CD6, and KiM8 antigens
- On electron microscopy: melanosomes within phagosomes

Mast cell (Fig. 33-8)

- Specialized secretory cells: originate in bone marrow from CD34 positive stem cells
- Proliferation depends on c-kit receptor and the stem cell factor (SCF) ligand
- Round/ovoid nucleus
- Granules can be secretory or lysosomal (0.2 to 0.5 μm)
- Mediators can be preformed and stored in granules (histamine, heparin, tryptase, chymase)
- Lattice-like structure of granules: found in mast cells of skin and intestinal submucosa
- Scroll-like structure of granules: found in mast cells of lung and intestinal mucosa

Collagen (Fig. 33-9)

- Fibers have regular banding pattern (periodicity) at approximately 70-nm intervals
- Regularly oriented fibers composed of fibrils and microfibrils
- Fibrils are aligned in a parallel manner, resulting in a pattern of cross-striations

Elastic Tissue (Figs. 33-10 and 33-11)

- Amorphous branching structures forming continuous sheets in some connective tissues
- Fibers composed of elastin with an electron-lucent core surrounded by thin, longitudinally oriented electron-dense microfibrils (Fig. 33-11)
- F = fibroblast; E = elastic tissue; C = collagen fibers (Fig. 33-10)

Eosinophil (Fig. 33-12)

- Nucleus has a deep groove and segment
- Granules contain electron-dense staining zone that is usually angulated or rectangular in shape surrounded by a lucent matrix
- Granules that contain the eosinophil basic proteins
 - Major basic protein (MBP)—only protein located in core
 - Eosinophilic cationic protein (ECP)—located in matrix

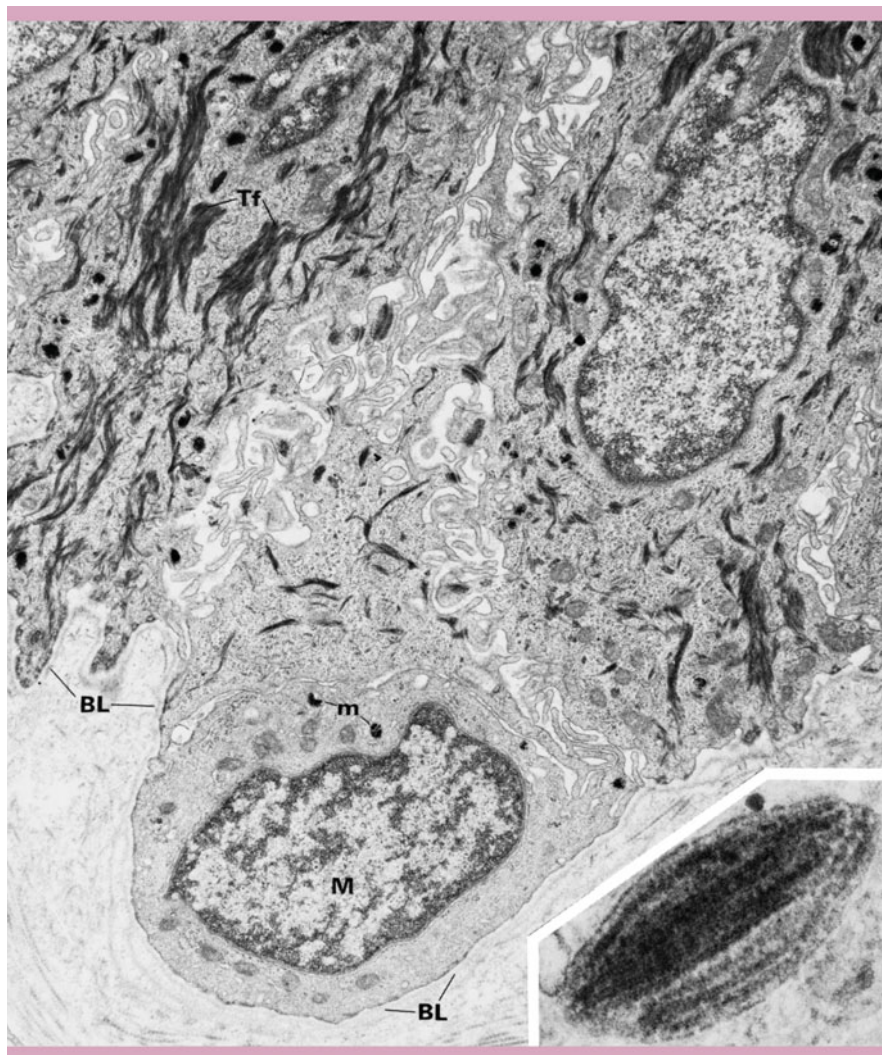


FIGURE 33-6 Melanocyte.
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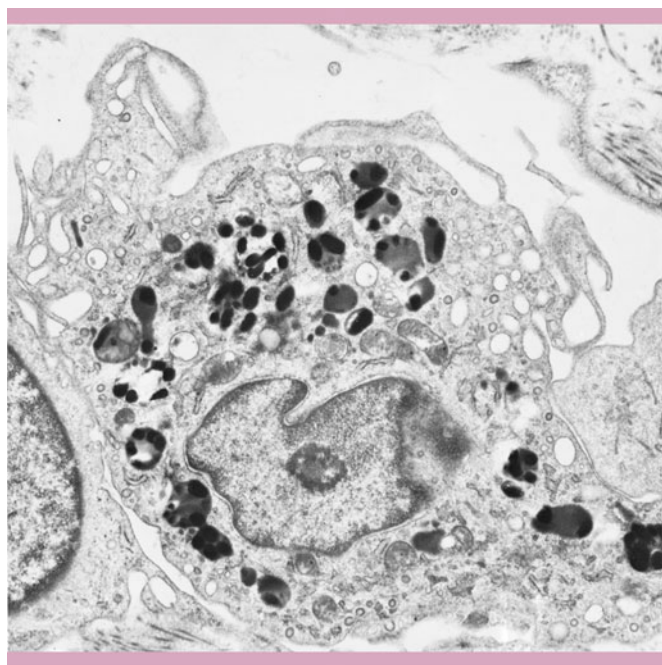
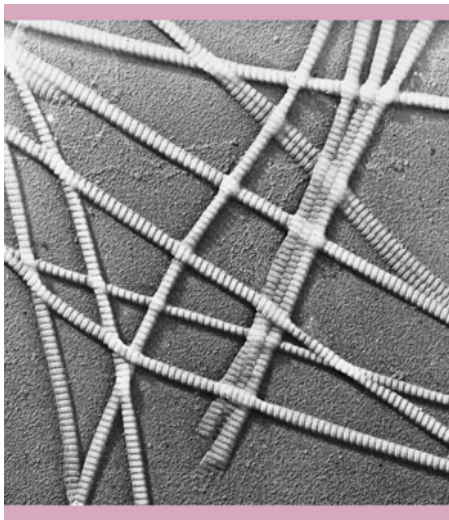
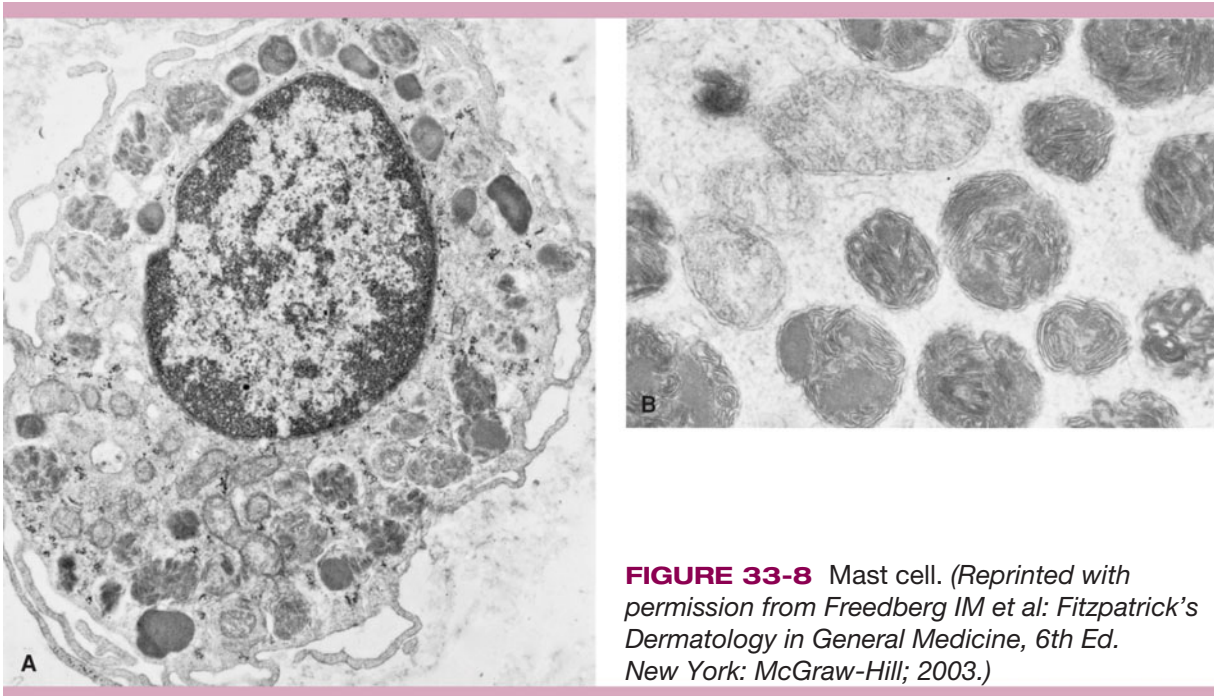


FIGURE 33-7 Macrophage. (Reprinted with permission
from Freedberg IM et al: *Fitzpatrick's Dermatology in
General Medicine*, 6th Ed. New York: McGraw-Hill; 2003.)



- Eosinophil-derived neurotoxin (EDN)—located in matrix
- Eosinophil peroxidase (EPO)—located in matrix

Amyloid

- Composed of nonfibrillary protein known as amyloid P component and a fibrillary component that is derived from various sources
- Has an antiparallel beta-pleated sheet configuration
- Amorphous moderately dense material located in extracellular spaces
- At higher magnification, short and haphazardly arranged filaments (7–15 nm) can be observed, like straw strewn on the ground

ULTRASTRUCTURAL FINDINGS IN DERMATOLOGIC CONDITIONS

Fabry Disease (Fig. 33-13)

- Deficient activity of lysosomal enzyme alpha-galactosidase-A
- Inherited as X-linked recessive; heterogenous females are generally asymptomatic, but may have characteristic corneal opacities
- Manifestations include: angiokeratomas in bathing suit distribution, acroparesthesia, acute attacks of pain, cardiovascular and renal disease
- Accumulation of neutral glycosphingolipids in most visceral tissues and body fluids, in particular endothelial cells

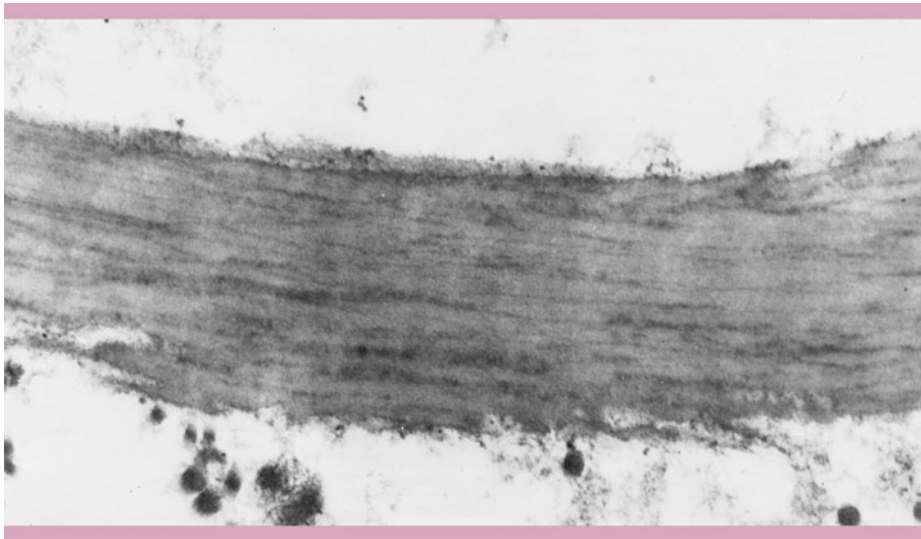


FIGURE 33-11 Elastic fibers in normal human skin. (Reprinted with permission from Wolff et al., *Fitzpatrick's Dermatology in General Medicine*, 7th Ed. New York: McGraw-Hill; 2008.)

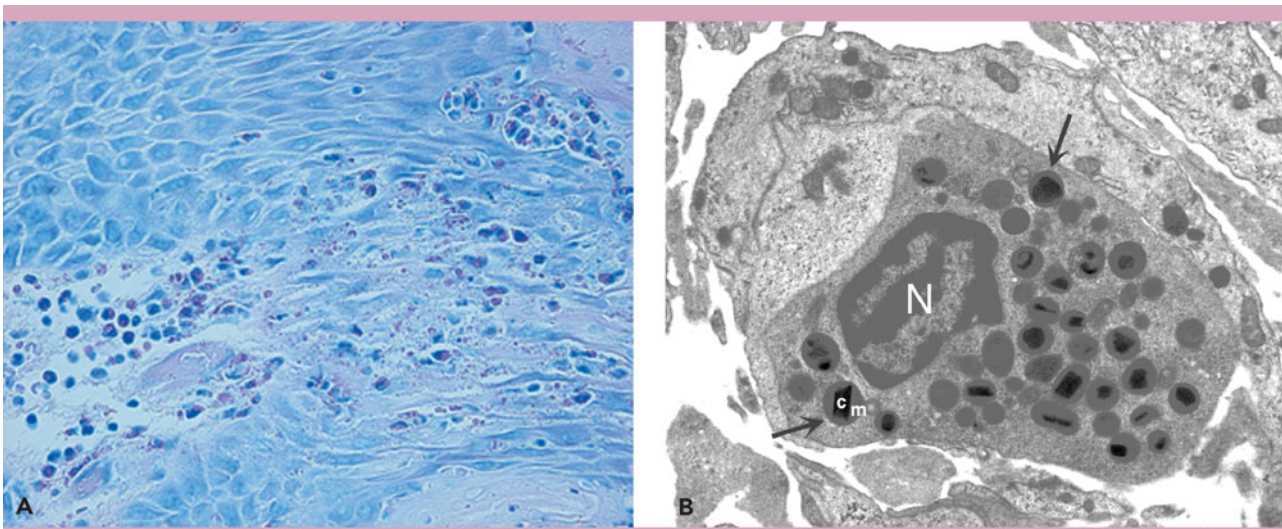


FIGURE 33-12 Eosinophil. (From Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003.)

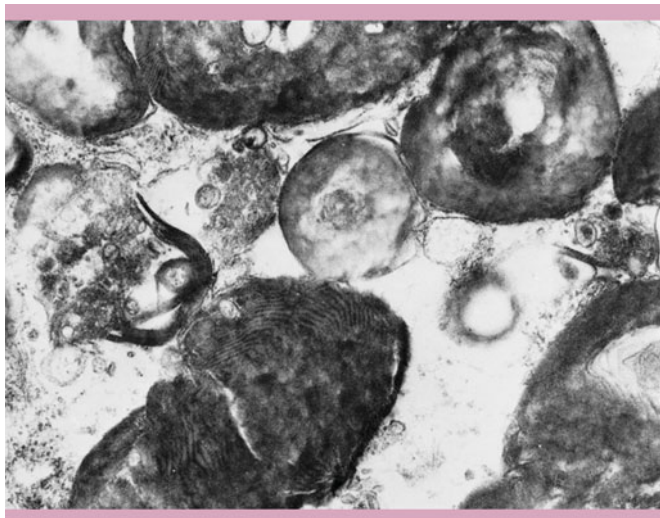


FIGURE 33-13 Mitral valve in Fabry's disease. (From Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003.)

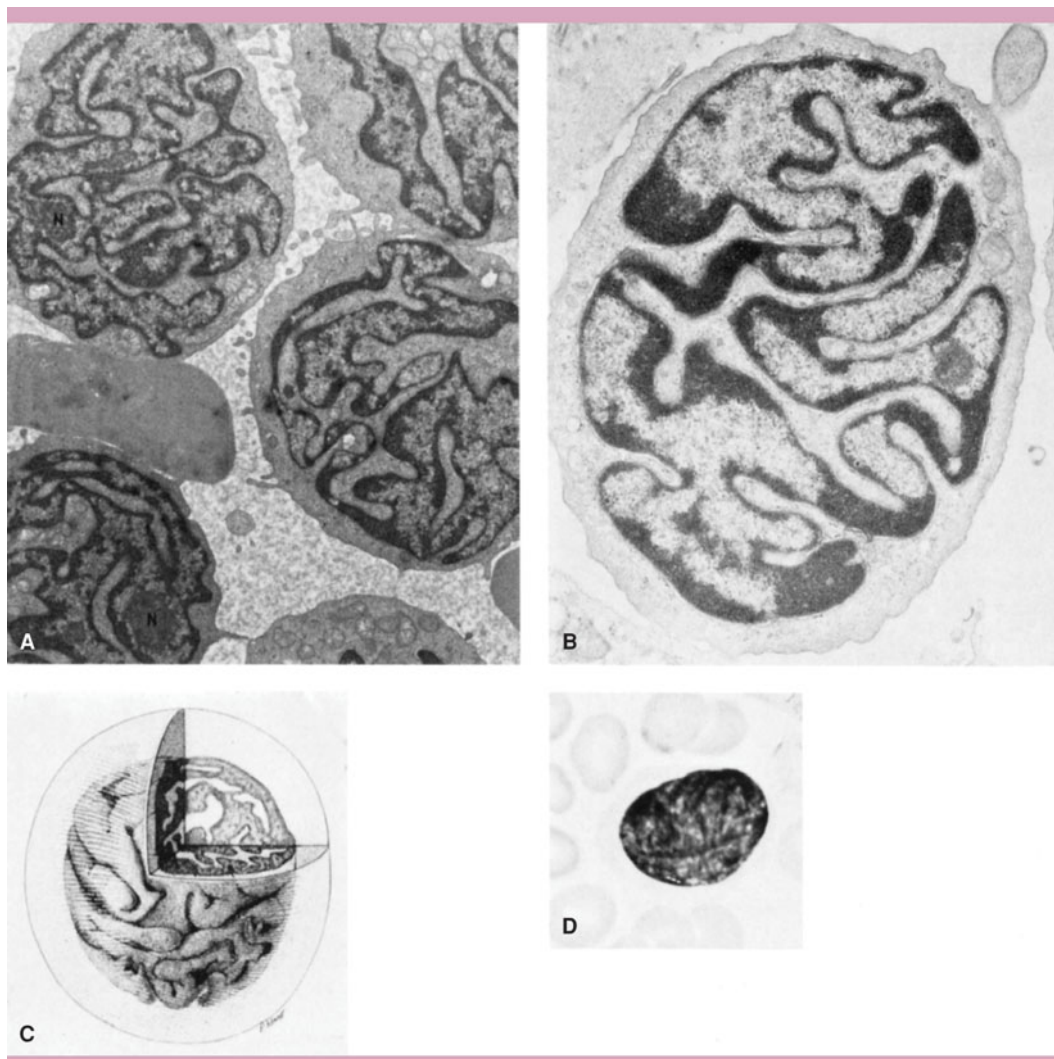


FIGURE 33-14 Sézary cell. (From Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003.)

- Concentric lamellar inclusions in lysosomes of fibrocytes

Mycosis Fungoides, Sézary Cell (Fig. 33-14)

- CD4 + T-helper lymphocytes
- Convoluted nucleus that is deeply indented (cerebriform)

Granular Cell Tumor

- Schwann cell origin
- Cytoplasmic granular appearance from numerous lysosomes, contain granular and membranous debris

INFECTIONS

Pox Virus (Fig. 33-15)

- Single molluscum contagiosum virus virion
- Size = 240×300 nm, no envelope
- dsDNA virus, capsid assembly in cytoplasm
- Also known to cause Orf, milker's nodules, variola, and vaccinia

Herpes Family of Viruses (Fig. 33-16)

- Size = 120 to 200 nm
- Icosahedral, enveloped dsDNA
- Replicates in nucleus
- Herpes simplex (types 1 and 2) (human herpes virus (HHV) 1, HHV2), varicella-zoster (HHV3), Epstein-Barr virus (HHV4), cytomegalovirus (HHV5), HHV6 (roseola infantum), HHV8 (Kaposi sarcoma, body cavity lymphoma, Castleman disease)

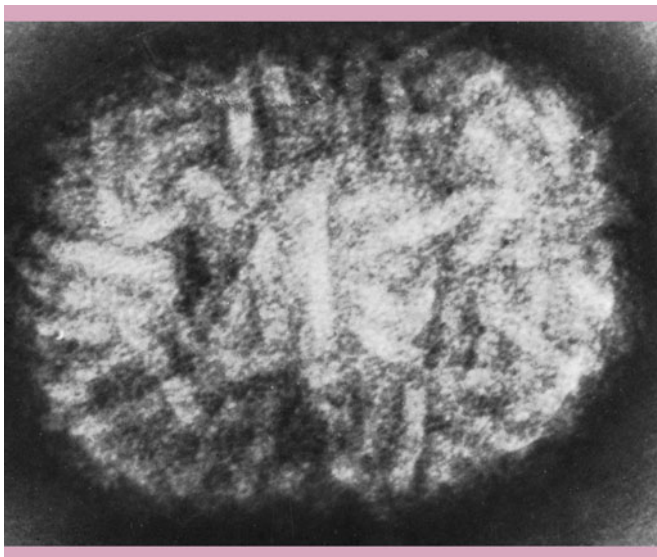


FIGURE 33-15 Pox virus. (From Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003.)

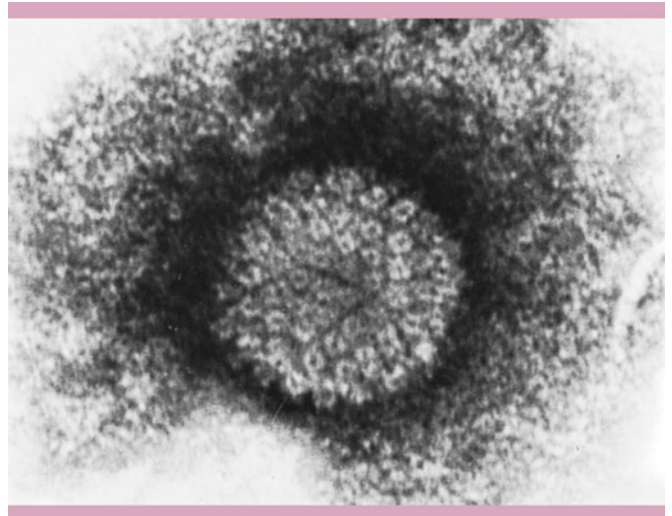


FIGURE 33-16 Herpes virus. (From Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003.)

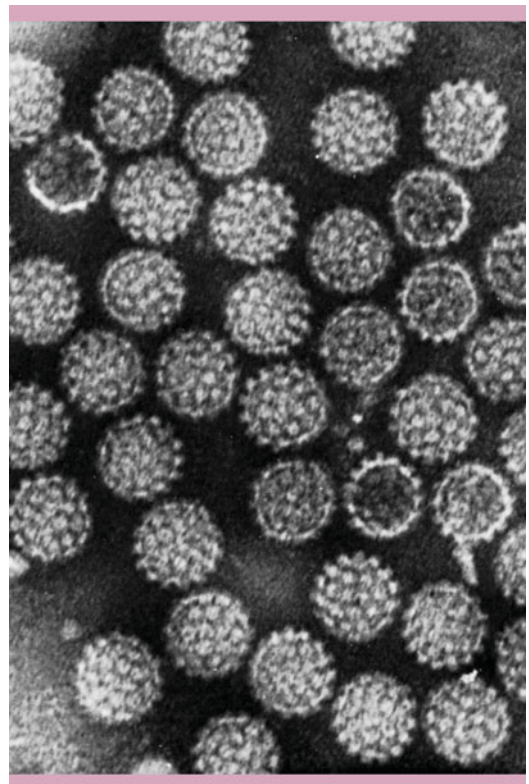


FIGURE 33-17 Papillomavirus. (From Freedberg IM et al: *Fitzpatrick's Dermatology in General Medicine*, 6th Ed. New York: McGraw-Hill; 2003.)

Papillomavirus (Fig. 33-17)

- Multiple nonenveloped virions
- Size: 50 to 55 nm, icosahedral with capsid subunits (capsome)
- Nonenveloped dsDNA replicates in nucleus

QUIZ

Questions

- Which study(s) should be performed to determine the precise location of separation in vesiculobullous conditions?
 - Hematoxylin and eosin stained tissue sections
 - Polarized light
 - Heat induced epitope retrieval
 - Electron microscopy
 - Laser microdissection
- You have just seen a male patient that has numerous angiokeratomas and acroparesthesias. To confirm the diagnosis, a biopsy is performed. For optimal tissue preservation of cellular detail, how should the tissue be submitted to pathology?
 - In formalin
 - In sterile saline
 - In bacteriostatic saline
 - In water
 - In glutaraldehyde
 - In Bouin solution
- Which description matches the ultrastructural appearance of a patient with a brown macule that hives when stroked?
 - Rod- and/or racquet-shaped cytoplasmic granule
 - Homogenous dense core cytoplasmic granule
 - Organized subepidermal plaque between two cells associated with keratin
 - Organized subepidermal plaque between one cell and the dermis
 - Scroll Like structure of granule
 - Fibers with periodicity of approximately 70 nm and aligned in a parallel manner
 - Granules with angulated or rectangular electron dense area
 - Convolute nucleus with deep indentions (cerebriform)
- Which description matches the ultrastructural appearance of a child with crusted purpuric papules and a scaly seborrheic-like eruption in the scalp and groin?
 - Rod- and/or racquet-shaped cytoplasmic granule
 - Homogenous dense core cytoplasmic granule
 - Organized subepidermal plaque between two cells associated with keratin
 - Organized subepidermal plaque between one cell and the dermis
 - Scroll-like structure of granule
- Fibers with periodicity of approximately 70 nm and aligned in a parallel manner
- Granules with angulated or rectangular electron dense area
- Convolute nucleus with deep indentions (cerebriform)
- Which description matches the ultrastructural appearance of an elderly person with tense bullae located on intertriginous areas and lower extremities that may be preceded by a hive without scarring?
 - Rod- and/or racquet-shaped cytoplasmic granule
 - Homogenous dense core cytoplasmic granule
 - Organized subepidermal plaque between two cells associated with keratin
 - Organized subepidermal plaque between one cell and the dermis
 - Scroll-like structure of granule
 - Fibers with periodicity of approximately 70 nm and aligned in a parallel manner
 - Granules with angulated or rectangular electron dense area
 - Convolute nucleus with deep indentions (cerebriform)
- Which description matches the ultrastructural appearance of a fair-skinned, male, 70-year-old patient with a solitary erythematous nodule on the face?
 - Rod- and/or racquet shaped cytoplasmic granule
 - Homogenous dense core cytoplasmic granule
 - Organized subepidermal plaque between two cells associated with keratin
 - Organized subepidermal plaque between one cell and the dermis
 - Scroll-like structure of granule
 - Fibers with periodicity of approximately 70 nm and aligned in a parallel manner
 - Granules with angulated or rectangular electron dense area
 - Convolute nucleus with deep indentions (cerebriform)
- Which description matches the ultrastructural appearance of a patient with persistent scaly patches in sun protected areas that respond poorly to topical steroids?
 - Rod- and/or racquet-shaped cytoplasmic granule
 - Homogenous dense core cytoplasmic granule
 - Organized subepidermal plaque between two cells associated with keratin
 - Organized subepidermal plaque between one cell and the dermis
 - Scroll-like structure of granule

- F. Fibers with periodicity of approximately 70 nm and aligned in a parallel manner
- G. Granules with angulated or rectangular electron dense area
- H. Convoluted nucleus with deep indentions (cerebriform)
8. Which description matches the ultrastructural appearance of a patient with hyperextensibility of the skin, easy bruisability, poor healing with fish mouth scars?
- A. Rod- and/or racquet-shaped cytoplasmic granule
- B. Homogenous dense core cytoplasmic granule
- C. Organized subepidermal plaque between two cells associated with keratin
- D. Organized subepidermal plaque between one cell and the dermis
- E. scroll like structure of granule
- F. Fibers with periodicity of approximately 70 nm and aligned in a parallel manner
- G. Granules with angulated or rectangular electron dense area
- H. Convoluted nucleus with deep indentions (cerebriform)
9. In which stage of development does the melanin appear in the melanosome?
- A. Stage I
- B. Stage II
- C. Stage III
- D. Stage IV
- E. Stage V
10. Which protein is not an intermediate filament?
- A. Desmin
- B. Actin
- C. Vimentin
- D. Keratin
- E. Neurofilament
2. E. Glutaraldehyde. Fixation with glutaraldehyde provides the best structural preservation; unlike formaldehyde, glutaraldehyde is slowly penetrating. Therefore, only very small pieces of tissue are processed (i.e., 0.5 to 1 mm³ or 2–3 mm² and thickness of about 0.5 mm). Electron microscopy may also be performed on formalin fixed material from deparaffinizing a wax block. Preservation may be sufficient for diagnostic purposes although results may be variable. Formalin is used for routine tissue fixation. Sterile saline is often used to submit tissue for microbiology studies. Bouin solution may be used to help tissue dyes adhere.
3. E. Scroll-like structure of granule. The patient has a mastocytoma that demonstrates Darier sign (hives when stroked). The characteristic cell is mast cells that contain scroll like structure of granules on electron microscopy.
4. A. Rod- and/or racquet-shaped cytoplasmic granule. The patient has findings that suggest Langerhans cell histiocytosis. The characteristic cell is the Langerhans cell that contains rod- and/or racquet-shaped cytoplasmic granules on electron microscopy.
5. D. Organized subepidermal plaque between one cell and the dermis. The patient has findings that suggest bullous pemphigoid, which affects proteins in the hemidesmosome.
6. B. Homogenous dense core cytoplasmic granule. The patient has findings that suggest Merkel cell carcinoma. The characteristic cell is the Merkel cell that contains homogenous dense core cytoplasmic granule on electron microscopy.
7. H. Convoluted nucleus with deep indentions (cerebriform). The patient has findings that suggest mycosis fungoides. The characteristic cell is the Sezary cell that contains a convoluted nucleus with deep indentions (cerebriform) on electron microscopy.
8. F. Fibers with periodicity of approximately 70 nm and aligned in a parallel manner. The patient has findings that suggest Ehlers-Danlos syndrome, which is a congenital abnormality of collagen. On electron microscopy, collagen appears as fibers with periodicity of approximately 70 nm and aligned in a parallel manner.
9. C. Stage III. There are only four stage of melanosome development. Melanosomes become elongated and form ordered, cross-striated lattice in stage II of development. Melanin does not appear until stage III. In stage IV, melanosomes are enriched with electron dense melanin; the lattice is obscured.
10. B. Actin. There are five main classes of intermediate filaments: cytokeratin, vimentin, desmin,

Answers

1. D. Electron microscopy. Electron microscopy is an ancillary technique to resolve diagnostic difficulties in human histopathology through examination of ultrastructural findings at the cellular and organelle level, such as meticulous examination of the dermal-epidermal junction to determine the location of separation in vesiculobullous diseases. Immunofluorescence is also helpful. Hematoxylin and eosin stained tissue sections is the standard method of preparation of tissue for light microscopy. Polarized light is used to confirm the presence of polarizable material (i.e., amyloid). Heat induced epitope retrieval may be necessary for immunohistochemistry of formalin fixed tissue.

neurofilament, and glial filament. Actin is a protein protein involved in the contractile apparatus of cells.

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HIGH-YIELD FACTS FOR THE DERMATOLOGY BOARDS

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The purpose of this chapter is to present information that may be considered “high yield” for the dermatology board exam, mock boards, and recertification exam.

Table 34-1 identifies common factoids relating to genetic inheritance of diseases. Table 34-2 focuses on important disease-associated viruses. Table 34-3 focuses on histologic bodies. Table 34-4 discusses infectious

diseases for which there are known vectors. Table 34-5 presents common contact allergens. Tables 34-6, 34-7, and 34-8 focus on common findings of the bones, eyes, and nails, respectively.

The information included herein should not be considered complete or exhaustive. Detailed descriptions of the topics are found in other chapters.

TABLE 34-1 Genes to Know

Disease	Gene/Protein		Gene Function
Incontinentia Pigmenti	XLD	(NEMO) NF-κB essential modulator	Transcription factor
AUTOSOMAL DOMINANT INHERITANCE			
Angioedema, hereditary (Quinke’s)	(C1INH) C1 esterase inhibitor		Inhibits first component of complement
Bannayan-Riley-Ruvalcaba	(PTEN) phosphatase and tensin homolog		Tumor suppressor
Bart’s syndrome	(COL7A1) type VII collagen		Anchoring fibril
Bullous ichthyosiform erythroderma (epidermolytic hyperkeratosis)	Keratins 1 and 10		Intermediate filament

Continued

TABLE 34-1 (Continued)

Disease	Gene/Protein	Gene Function
Bullous ichthyosis of Siemens	Keratin 2e	Intermediate filament
Carney complex (LAMB [lentigenes, atrial myxoma, mucocutaneous myxomas, blue nevi], NAME [nevi, atrial myxoma, myxoid neurofibroma, ephilides])	(<i>PRKAR1A</i>)	R1 regulatory subunit of protein kinase A
Cowden's syndrome (multiple hamartoma syndrome)	(<i>PTEN</i>)	Tumor suppressor
Darrier-White disease (keratosis follicularis)	(<i>SERCA2</i>) calcium ATPase2A2	Calcium dependent ATPase
Dyskeratosis congenita	(<i>DKC1</i> gene) dyskerin (<i>TERC</i>) telomerase, RNA component	rRNA processing Telomerase RNA component
Ectodermal dysplasia, hidrotic (Clouston's)	Connexin 30/ <i>ED2</i> gene, <i>HED</i> gene	Gap junction protein
Ectodermal dysplasia with skin fragility	Plakophilin 1	Structural
Epidermolysis bullosa, dominant dystrophic (EB)	(<i>Col7A1</i>) Type VII collagen	Anchoring fibril
Epidermolysis bullosa simplex (EBS)	Keratins 5 and 14	Intermediate filament
Erythrokeratoderma variabilis (EKV)	Connexin 31	Gap junction protein
Gardner's syndrome	(<i>APC</i>) adenomatosis polyposis coli	Cleaves β -catenin
Hailey-Hailey disease	(<i>ATPase2C1</i>)	Calcium-dependent ATPase
Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu)	Endoglin Alk-1 gene activin receptor binding kinase	TGF- β binding protein TGF- β receptor
MEN I	(<i>MEN1</i>) menin gene	Binds nuclear junD
MEN IIa and IIb	(<i>RET</i>) receptor tyrosine kinase	Proto-oncogene
Milroy's disease (Nonne-Milroy-Meige Syndrome)	(<i>FLT-4</i>) a.k.a (VEGFr-3)	Growth factor receptor
Monilethrix	KRT hHb6 and hHb1 Type II human hair keratins, 6 & 1	Intermediate filament
Muir-Torre syndrome	(<i>hMSH2</i>)	Mismatch repair gene
Nail-Patella syndrome	<i>LMX1B</i> gene	Homeobox domain transcription factor

Continued

TABLE 34-1 (Continued)

Disease	Gene/Protein	Gene Function
Naxos disease	Junctional plakoglobin Keratin 9	Structural protein Intermediate filament
Neurofibromatosis I	NF-1 (neurofibromin)	Increases GTPase activity of <i>ras</i>
Neurofibromatosis II	NF-2 (schwannomin or Merlin)	
NOMID syndrome (neonatal onset multisystem inflammatory disease); also called CINCA syndrome	CIAS1 gene	Cryopyrin gene, role in innate immune response.
Pachyonychia congenita	K6, K16, or K17	Intermediate filament
Peutz-Jeghers syndrome	STK11	Tumor suppressor
Piebaldism	(C-kit)	Proto-oncogene (tyrosine kinase)
Porphyria cutanea tarda	Uroporphyrinogen decarboxylase	
Porphyria, acute intermittent	Porphobilinogen deaminase	
Porphyria, erythropoietic protoporhyria (EPP)	Ferrochelatase	Mitochondrial gene
Porphyria, variegate	Protoporphyrinogen oxidase	Mitochondrial gene
Reed syndrome (cutaneous and uterine leiomyomatosis)	Fumarate hydratase	Tumor suppressor
Rubenstein-Taybi syndrome	(CBP) CREB-Binding Protein	Involved in cAMP regulated gene expression
Striate PPK 1	Desmoglein-1	Structural protein
Striate PPK 2	Desmoplakin	Structural protein
Tuberous sclerosis	(TSC1) on Chrom. 9 hamartin gene (TSC2) on Chrom. 16 tuberlin gene	GTPase activating protein domain
Vohwinkel	Loricrin gene	Structural
Vohwinkel with deafness	Connexin 26	Gap junction protein
Vorner syndrome	Keratin 9	Intermediate filament
Waardenburg syndrome	(PAX3) (MITF) (EDN3/SOX10) – with Hirschprung's	Transcription factor Transcription factor endothelin
White sponge nevus	KERATIN 4 and 13	Intermediate filament

Continued

TABLE 34-1 (Continued)

Disease	Gene/Protein	Gene Function
Autosomal Recessive Inheritance		
Atrichia with papules (“alopecia universalis”)	(<i>HR</i>) hairless gene	Zinc finger
Albinism I, oculocutaneous	TYR-tyrosinase	Melanin pathway
Albinism II, oculocutaneous	<i>P</i> gene—pink protein	Unknown
Albinism III, oculocutaneous (rufous)	(<i>TYRP1</i>) tyrosinase-related protein 1	Stabilizes tyrosinase
Alkaptonuria	(<i>HGO</i>) homogentisic acid oxidase	Phenylalanine and tyrosine breakdown pathway
Ataxia-telangiectasia (Louis-Bar)	(<i>ATM/ATM</i> protein) ataxia-telangiectasia mutated	Phosphatidylinositol-3-kinase like domain
Basal cell carcinoma syndrome, nevoid (Gorlin)	(<i>PTCH</i>) <i>patched</i> homolog (<i>Drosophila</i>)	Inhibits “smoothened” signaling; this inhibition blocked by “hedgehog”
Bloom’s syndrome	(<i>BLM</i>)	DNA helicase
Chediak-Higashi syndrome	<i>LYST/CHS1</i> gene/ <i>CHS</i> protein	Lysosomal transport
Citrullinemia	(<i>ASS</i>) arginosuccinate synthetase gene	Enzyme in urea cycle
Cockayne’s syndrome	(<i>CKN1</i>) (<i>ERCC6</i>) <i>XPB</i> DNA helicase	DNA helicase—DNA repair
Epidermolysis bullosa, generalized atrophic benign (GABEB)	(<i>BPAg2</i>) collagen XVII (<i>LAMB3</i>) laminin	Structural protein
Epidermolysis bullosa, junctional (EB with pyloric atresia)	Integrin $\alpha 6, \beta 4$ / <i>ITGB6</i> gene, <i>ITBG4</i> gene	Structural
Epidermolysis bullosa, junctional (EB letalis, Herlitz)	Laminin 5 <i>LAMA3</i> , <i>LAMB3</i> , <i>LAMC2</i> genes	Structural
EBS with muscular dystrophy	Plectin/ <i>PLEC1</i> gene	Structural
Familial Mediterranean fever	(<i>MEFV</i>) marenstrin	PMN inhibitor
Farber’s disease (lipogranulomatosis)	Acid ceramidase	Deficiency leads to ceramide accumulation
Gaucher’s disease	β -Glucocerebrosidase	
Griscelli syndrome	(<i>MTO5a</i>) myosin Va	Melanosome transport to keratinocytes

Continued

TABLE 34-1 (Continued)

Disease	Gene/Protein	Gene Function
Homocystinuria	Cystathione synthetase	Condensation of homocysteine and serine
Hurler's syndrome	Alpha-L-uronidase	
Hypotrichosis, localized autosomal recessive	(DSG4) desmoglein 4	Desmosomal cadherin
Ichthyosis, lamellar	Transglutaminase-1	
Lhermite-Duclos syndrome	(PTEN)	Tumor suppressor
Neimann-Pick disease	Sphingomyelinase	
Netherton's syndrome	SPINK5 gene	Serine protease inhibitor
Papillon-Lefevre syndrome	Cathepsin C	Lysosomal protease
Phenylketonuria	Phenylalanine hydroxylase	
PIBIDS syndrome	(XPD) (TFIIH) xeroderma pigmentosa D	DNA helicase
Porphyria, congenital erythropoietic (Gunther)	Uroporphyrinogen III cosynthase	
Porphyria, erythropoietic protoporhyria (EPP)	Ferrochelatase	Mitochondrial gene
Refsum syndrome	Phytanoyl Co-A hydroxylase	
Richner-Hanhart syndrome	Tyrosine aminotransferase	
Rothman-Thompson (poikiloderma congenital)	(RECQL4) DNA helicase	DNA helicase
Sjögren-Larsson syndrome	Fatty aldehyde dehydrogenase	
Takahara disease	Catalase	Bacterial defense
Tangier disease	(CERP)	Cholesterol efflux regulatory protein
Werner syndrome	(WRN) (ERCC) (XPB, D, and G)	DNA helicase
X-Linked Dominant Inheritance		
CHILD syndrome (congenital hemidysplasia with ichthyosiform erythroderma and limb defects)	(EBP gene) emopamil binding protein/ (NSDHL gene) 3-beta hydroxy sterol dehydrogenase	Cholesterol biosynthetic pathway
Conradi-Hünemann syndrome	(EBP) (PEX7)	Sterol isomerase peroxisomal gene
Incontinentia pigmenti	(NEMO) NF-κB essential modulator	Transcription factor

Continued

TABLE 34-1 (Continued)

Disease	Gene/Protein	Gene Function
X-Linked Recessive Inheritance		
Bruton's agammaglobulinemia	(<i>BTK</i> gene)	Tyrosine kinase
Ectodermal, dysplasia, hypohidrotic (Christ-Seimens-Touraine syndrome)	Ectodysplasin	
Fabry's disease (angiokeratoma corporis diffusum)	Alpha-galactosidase A	Hydrolyzes glycolipids and glycoproteins
Granulomatous disease of childhood, chronic	(<i>CYBB</i> gene) cytochrome B	NADPH-oxidase complex component (respiratory burst) needed to kill catalase-positive bacteria
Hunter's syndrome	Iduronate sulfatase	
Ichthyosis, X-linked	Aryl sulfatase C	Steroid sulfatase
Lesch-Nyhan syndrome	(<i>HGPRT</i>)	Purine salvage pathway enzyme
Menke's kinky hair syndrome	MNK	Copper transporting ATPase
SCID (severe combined immunodeficiency disease)	(<i>ADA</i>) adenosine deaminase II-2 receptor	
Wiskott-Aldrich syndrome	(<i>WASP</i>) (sialoglycoprotein)	Binds GTPase and actin
Unknown or No Inheritance Pattern		
Atopic dermatitis	Fillagrin (FLG)	Filament aggregating protein
Baere-Stevenson syndrome	(<i>FGFr2</i>) FGF receptor 2	
McCune-Albright syndrome	(<i>Gs-α</i>)	Stimulates G protein increasing cAMP

TABLE 34-2 Viruses

Associated or Causative Virus	Disease	Description
Coxsackie virus A-16	Hand-foot-and-mouth disease	Fever, ulcerovesicular stomatitis, acral erythematous vesicles, buttock lesions
Coxsackie viruses (A-10)	Herpangina	Fever, painful ulcerations in mouth
EBV (Epstein-Barr virus)	Oral hairy leukoplakia	Corrugated white plaque on lateral tongue common in AIDS
EBV, HBV, echovirus 6	Unilateral laterothoracic exanthem	Simulates zoster
Echovirus 16	Boston exanthema	Mild exanthematous febrile illness with aseptic meningitis
Echovirus 25 and 32	Eruptive pseudoangiomatosis	As per syndrome name
Enterovirus 71	Herpangina	Fever, painful ulcerations in mouth
Hepatitis B virus	Gianotti-Crosti syndrome	Children with sudden onset of lichenoid papules on face, extremities, and buttocks, sparing trunk
Hepatitis C virus	Lichen planus	Purple polygonal, plateau-shaped, pruritic, papules
HHV (human herpesvirus)-8	Castleman disease	Angiolymphoid hyperplasia usually plasmacytoid in lymph nodes
HHV-6	Rosai-Dorfman	Sinus histiocytosis with massive lymphadenopathy
HHV-6 and 7	Roseola infantum (exanthum subitum, sixth disease)	Infants with high fever followed by exanthema
HHV-7?	Pityriasis rosea	Usually asymptomatic well-known exanthema
HHV-8	Kaposi sarcoma	Vascular tumor, various types
HPV (human papilloma virus) 16 and 18, mostly	Bowen disease	Squamous cell carcinoma in situ
HPV (papovavirus-dsDNA) Low risk: Types 6 and 11 High risk: Types 16 and 18	Condyloma acuminata	Genital warts
HPV 1	Myrmecia	Large cup-shaped palmoplantar warts
	Verruca plantaris	(Plantar warts)
HPV 13 and 32	Heck disease (focal epithelial hyperplasia)	Small white and pink papules in mouth

Continued

TABLE 34-2 (Continued)

Associated or Causative Virus	Disease	Description
HPV 16	Bowenoid papulosis	Genital papules and plaques resembling Bowen's disease
HPV 2	Verruca vulgaris	Common warts
HPV 23b	Stucco keratoses	White hyperkeratotic plaques on legs
HPV 3	Verruca plana	(Flat warts)
HPV 5, 8, 12, and others as well as common types	Epidermodysplasia verruciformis	Inherited disorder of HPV infection and SCCs
HPV 6 and 11	Buschke and Löwenstein	Giant condyloma
HPV 60	Ridged wart	Wart with preserved dermatoglyphics
HPV 7b	Butcher's wart	Warty lesions seen in people who handle raw meat
HSV (herpes simplex virus)	Kaposi varicelliform eruption (eczema herpeticum)	Diffuse HSV ulcerations in eczematous dermatitis
MCV (molluscum contagiosum virus) -1 to MCV-4; MCV-2 in HIV	Molluscum contagiosum	Umbilicated lesions common in children and HIV
Nonspecific: hep. B, parvovirus B19, rubella	STAR complex	Sore throat, arthritis, rash
Paramyxovirus (RNA)	Measles (rubeola)	Viral prodrome, then enanthem (Koplick spots), then maculopapular rash spreading craniocaudally
Parapoxvirus	Orf	Umbilicated nodule after farm animal exposure
Parvovirus B19	Erythema infectiosum (fifth disease)	Slapped cheeks, reticular exanthem, anemia
Parvovirus B19	Papular/purpuric stocking-glove syndrome	As named
Poxvirus (DNA)	Molluscum contagiosum	Umbilicated lesions common in children and HIV
Togavirus (RNA)	Rubella	Viral prodrome, prominent lymphadenopathy, pain with superolateral eye movements, morbilliform rash, exanthem (Forschheimer's spots)
Variola (poxvirus) (DNA)	Variola major (smallpox)	12-day incubation, fever and malaise, then centrifugal vesiculopustular rash

TABLE 34-3 Histologic Findings

Disease	Histologic Finding	Description
A-HSV, CMV (cytomegalovirus), and VZV (varicella zoster virus) B-polio	Cowdry type A and B inclusion bodies	Type A: intranuclear eosinophilic, amorphous bodies surrounded by a clear halo Type B: in neuronal cells
Amiodarone hyperpigmentation	Lipofuscin granules	Yellow-brown granules in macrophages
Androgenic alopecia	Arao-Perkins bodies	Elastin bodies seen within “streamers” beneath vellus follicles
Benign cephalic histiocytosis	Comma-shaped bodies	Cytoplasmic bodies seen on EM
Café-au-lait macules, neurofibromatosis, Chediak-Higashi	Macromelanosomes	Large melanosomes
Chediak-Higashi	Giant liposomes in neutrophils	Large liposomal granules
Chromomycosis	Medlar/sclerotic bodies	Large (5-12 μ m round, thick walled brown cells seen in and out of giant cells)
Cutaneous meningioma	Psammoma bodies	Concentrically laminated calcified basophilic bodies
Cutaneous T-cell lymphoma	Pautrier microabscess	Clusters of lymphocytes within epidermis
Darier’s, Grover’s, warty dyskeratoma (Hailey-Hailey)	Corps grains Corps ronds	Dyskeratotic keratinocytes with elongated nuclei seen in the granular zone Dyskeratotic keratinocytes with perinuclear halo and surrounding basophilic dyskeratotic material
Ehrlichiosis	Morulae	Leukocyte intracytoplasmic inclusions
Farber’s disease	Farber bodies	Curvilinear bodies seen in the cytoplasm of fibroblasts and endothelial cells on EM
Farber’s disease and other ganglioside storage diseases	Zebra bodies	Vacuoles with transverse membranes in endothelial cells on EM
Granular cell tumors	Pustulo-ovoid bodies	Round cytoplasmic eosinophilic inclusions
Granuloma inguinale	Donovan bodies	Intrahistiocyte inclusions comprised of organisms that stain positively with Warthin-Starry stain or Giemsa

Continued

TABLE 34-3 (Continued)

Disease	Histologic Finding	Description
HTLV-1 (human T-cell lymphotropic virus-1) and ATL (adult T-cell lymphoma/leukemia)	Flower bodies/cells	Atypical CD4 + T cells
Interface dermatitis	Civatte/colloid bodies	Apoptotic keratinocytes that may be found in epidermis or extruded into papillary dermis
Interface dermatitis, especially LP	Max-Joseph space	Artifactual separation between dermis and epidermis
Langerhans cells	Birbeck granules	Racquet-shaped bodies seen on EM
Lepromatous leprosy	Globi	Collections of AFB (acid fast bacilli) seen in foamy macrophages with Fite stain
Lipoid proteinosis	Onion skinning	Hyaline material surrounding blood vessels
Malakoplakia	Michaelis-Gutman bodies	Calcified lamellar eosinophilic bodies in foamy “ von Hansemann” macrophages
Molluscum contagiosum	Henderson-Patterson bodies	Cytoplasmic eosinophilic inclusions in keratinocytes
Normal endothelial cells	Weibel-Palade bodies	Organelles seen on EM
Normal skin, absent in harlequin fetus	Lamellar/Odland bodies	Free fatty acid, ceramide, and cholesterol containing vacuoles released from the golgi in the stratum granulosum seen on EM
Ochronosis	Banana bodies	Crescentic banana-shaped pigmented bodies in the upper dermis
Ovarian neoplasms	Psammoma bodies	Concentrically laminated calcified basophilic bodies
Plasmacytoid proliferations (e.g., multiple myeloma)	Dutcher bodies	Intranuclear inclusions of immunoglobulins
Pleomorphic lipoma	Floret cells	Multinucleated giant cells with radially arranged nuclei
Porphyria cutanea tarda, pseudoporphyria, and erythropoietic protoporphyria	Caterpillar bodies	Eosinophilic wavy collection in basal layer of epidermis, found on roof of blister
Protothecosis	Mulberry bodies	Thick-walled spherical body containing organisms
Rabies	Negri bodies	Eosinophilic bodies within large neurons
Rhinoscleroma	Mikulicz cell	Foamy macrophage containing bacteria
Rhinoscleroma	Russel bodies	Immunoglobulin inclusions in plasma cells

Continued

TABLE 34-3 (Continued)

Disease	Histologic Finding	Description
Sarcoidosis, botryomycosis, sporotrichosis, actinomycosis, other	Asteroid bodies	Stellate collections of eosinophilic spicules and giant cells
Sarcoidosis and other granulomatous diseases	Conchoidal bodies (Schaumann bodies)	Shell-like calcium complexes within giant cells
Schwannoma	Antoni A tissue	Cellular areas with Verocay bodies
	Antoni B tissue	Loose stromal area with relative paucity of cells
	Verocay bodies	Palisading nuclei arranged in rows with peripheral eosinophilic cytoplasm
Sclerema neonatorum and subcutaneous fat necrosis of the newborn	Cholesterol clefts	Needle-like crystals in fat cells
Spitz nevus	Kamino bodies	Eosinophilic bodies composed of BMZ (basement membrane zone) material
Sporotrichosis	Cigar bodies	Budding cigar-shaped PAS+ yeast (rarely seen)
Thyroid neoplasms	Psammoma bodies	Concentrically laminated calcified basophilic bodies
Well's syndrome, arthropod bites, other	Flame figures	Dermal eosinophils and eosinophilic granules surrounding central masses of brightly pink amorphous collagen

TABLE 34-4 Infectious Diseases and Their Vectors

Organism	Vector	Disease
<i>Ancylostoma brazilienses</i>	Feces, animal	Cutaneous larva migrans
Arbovirus, RNA-virus	Food, contaminated	West Nile fever
<i>Bartonella bacilliformis</i>	<i>Lutzomyia verrucarum</i> (sandfly)	Carrion disease
<i>Bartonella quintana</i>	<i>Pediculus humanus</i> (louse)	Trench fever
<i>Borrelia afzelii</i>	<i>Ixodes ricinus</i>	Acrodermatitis chronica atrophicans
<i>Borrelia burgdorferi</i>	<i>Ixodes scapularis</i> (<i>dammini</i>) (Northeast and Midwest U.S.) <i>Ixodes pacificus</i> (Western U.S.)	Lyme disease
<i>Borrelia duttonii</i> , <i>B. recurrentis</i>	<i>Orrithodorus tholozanii</i> (tick) <i>Pediculus humanus</i> (louse)	Relapsing fever
<i>Borrelia garinii</i> and <i>B. afzelii</i>	<i>Ixodes ricinus</i> (Europe)	Lyme disease

Continued

TABLE 34-4 (Continued)

Organism	Vector	Disease
<i>Burkholderia pseudomallei</i>	Swamp water	Melioidosis (Whitmore disease)
Cercariae of <i>Schistosomes</i> (nonhuman)	Snails	Cercarial dermatitis
<i>Dermatobia hominis</i> (botfly) and <i>Cordylobia</i> species	Mosquito	Myiasis
<i>Dracunculus medinensis</i>	<i>Cyclops</i> water flea in drinking water	Dracunculiasis (guinea worm disease, medina worm)
<i>Ehrlichia chaffeensis</i>	Tick bites	Ehrlichiosis
<i>Erysipelothrix rhusiopathiae</i>	Found on pigs, shellfish, and turkeys	Erysipeloid of Rosenbach
<i>Francisella tularensis</i>	<i>Amblyomma americanum</i> (lone star tick) <i>Chrysops discalis</i> (deer fly) <i>Dermacentor andersonii</i> (tick) (from handling wild rabbits)	Tularemia (Ohara disease, deer fly fever)
<i>Leishmaniasis mexicana</i> ; <i>L. braziliensis braziliensis</i> ; <i>L. braziliensis guyanensis</i> ; <i>L. braziliensis panamensis</i>	<i>Lutzomyia</i> (sandfly)	Leishmaniasis, new world
<i>L. tropica</i> ; <i>L. major</i> ; <i>L. aethiopia</i> ; <i>L. infantum</i>	<i>Phlebotamus perniciosus</i> (sandfly) Reservoir: Rodents (gerbils)	Leishmaniasis, old world
<i>Leishmaniasis mexicana</i>	<i>Lutzomyia flaviscutellata</i>	Chiclero ulcer
<i>Leptospira interrogans ictero haemorrhagiae</i>	Rat urine	Weil disease
<i>Loa loa</i>	<i>Chrysops</i> species (mango fly or deer fly)	Loiasis (Calabar, tropical and fugitive swelling)
<i>Nocardia farcinica</i>	Cattle	Bovine farcy
<i>Onchocerca volvulus</i>	<i>Simulium</i> species (black fly)	Onchocerciasis (river blindness)
<i>Pseudomonas mallei</i>	Horses, mules, and donkeys	Glanders (Farcy)
<i>Rickettsia akari</i>	<i>Allodermanyssus sanguineus</i> (house mouse mites) <i>Liponyssoides sanguineus</i> (house mouse mites) Reservoir: <i>Mus musculus</i> (house mouse)	Rickettsialpox
<i>Rickettsia conorii</i>	<i>Rhipicephalus sanguineus</i> (dog tick)	Mediterranean fever (boutonneuse fever, South African tick bite fever)
<i>Rickettsia prowazekii</i>	<i>Pediculus humanus</i> (body louse) Reservoir: <i>Glaucomys volans</i> (flying squirrel)	Typhus, epidemic

Continued

TABLE 34-4 (Continued)

Organism	Vector	Disease
<i>Rickettsia rickettsii</i>	<i>Amblyomma americanum</i> (lone star tick) <i>Dermacentor andersoni</i> , <i>D. variabilis</i> Ixodid ticks	Rocky Mountain spotted fever
<i>Rickettsia tsutsugamushi</i>	<i>Trombiculid</i> red mite (chigger)	Scrub typhus (tsutsugamushi fever)
<i>Rickettsia typhi</i>	<i>Xenopsylla cheopis</i> (rat flea)	Typhus, endemic
<i>S. mansoni</i> , <i>S. haematobium</i> , and <i>S. japonicum</i>	Snails	Schistosomiasis
<i>Spirillum minor</i> , <i>Streptobacillus</i> <i>moniliformis</i>	Rat bites	Rat-bite fever (Haverhill fever, Sodoku)
<i>Spirometra</i> (dog and cat tapeworm larvae)	Frogs and snakes (application or ingestion)	Sparganosis
<i>Taenia solium</i>	Contaminated food	Cystercercosis cutis
<i>Toxoplasma gondii</i>	Cat feces and undercooked meat	Toxoplasmosis
<i>Trichinella spiralis</i>	Pig, bear, and walrus meat	Trichinosis
<i>Trypanosoma cruzi</i>	Reduviid bug (assassin bug, kissing bug)	Chagas disease (American trypanosomiasis)
<i>Trypanosoma gambiense</i> , <i>Trypanosoma rhodesiense</i>	Tsetse fly (<i>Glossina morsitans</i>)	African trypanosomiasis
<i>Wuchereria bancrofti</i> , <i>Brugia</i> <i>malayi</i> , <i>Brugia timori</i>	Culex, Aedes, and Anopheles mosquitos	Elephantiasis tropica
<i>Yersinia pestis</i>	<i>Xenopsylla cheopis</i> (rat fleas)	Plague

TABLE 34-5 Contact Allergens

Common Sources	Allergen	Other Information
Animals	Bermuda fire sponge	Contact erythema multiforme
Cement	Potassium dichromate	
Clothing	Formaldehyde	permanent-press textile products
Clothing snaps	Nickel sulfate	Eyelid dermatitis, dimethylglyoxime test (pink)
Coloring, blue	Cobalt dichloride	Nickel plating, hair dye, metal, vitamin B ₁₂ , cement, construction
Cosmetics	Ammonium persulfate	Hair bleach
	Benzalkonium chloride (Quaternium 15)	Shampoos
	Formaldehyde	

Continued

TABLE 34-5 (Continued)

Common Sources	Allergen	Other Information
	Glyceryl thioglycolate	Permanent (hair) wave solutions
	Methyl methacrylate	Artificial nails, dental work
	Paraphenylenediamine	Dark hair dye, henna tattoo additive
	toluenesulfonamide/ formaldehyde resin	Nail lacquer/hardener: eyelid dermatitis
	Imidazolidinyl urea (Germall 115)	Formaldehyde releaser found in cosmetics
Cyanoacrylate	Ethyl cyanoacrylate	
Flavoring; additives	Cinnaminic aldehyde	Pastries, toothpaste, chewing gum, beverages, Bitters, lipstick
Food	Ammonium persulfate	Bleaching agent in flour
	Benzoyl peroxide	Bleaching agent in flour
	Diallyl disulfide	Garlic
	Eugenol	Cloves
	Sesamine	Sesame oil
Fragrance, adhesives, flavoring	Balsam of Peru	Cross reacts with cinnamon, clove, orange peel, benzoin
Glues, plastics	Epoxy resin	
Jewelry	Na gold-thiosulfate	Best screen for allergy to gold; Late and persistent positive reactions
Jewelry, clothing snaps	Nickel sulfate	Eyelid dermatitis, dimethylglyoxime test (pink)
Leather	Chromates potassium dichromate	
Medications	Benzocaine	Topical amide anesthetics
	Benzoyl peroxide	Acne medication
	Budesonide	Screening for Group B and D corticosteroids
	Ethylenediamine	Stabilizer in Mycolog; cross-reacts with aminophylline and hydroxyzine
	Glutaraldehyde	Cold sterilant
	Hydrocortisone-17-butyrate	Group B and D corticosteroids
	Neomycin sulfate	Topical antibiotic
	Tixocortol pivalate	Group A corticosteroids

Continued

TABLE 34-5 (Continued)

Common Sources	Allergen	Other Information
Plants	Allylisothiocyanate	Mustard, radish
	Calcium oxalate crystals	Dieffenbachia (“dumb cane”)
	D-Uscnic acid	Lichen
	Furocoumarin	Celery, dill, fig, lime, parsley, parsnip, meadow grass, St. John’s wort (Umbelliferae family)
	Limonene	Orange and lemon peel, tea tree oil
	Primin	Primrose (<i>Primula obonica</i>)
	ricin	Castor bean (<i>Ricinus communis</i>)
	Sesquiterpene lactone	Compositae family members (chrysanthemum, ragweed, artichoke)
	Tuliposide A	Peruvian lily, tulip
	Urushiol	Poison ivy, poison oak, poison sumac, Japanese lacquer tree, cashew nut, mango, ginkgo tree
Plaster	Potassium dichromate	
Preservatives	Kathon CG (methylchloro-isothiazolinone)	Found in cosmetics, formaldehyde-like
	Methylchloroisothiazolinone (Kathon CG)	Used in cosmetics
	Paraben mix	Low incidence of contact dermatitis
	Quaternium-15 (most common preservative cause of AD)	Formaldehyde releasing preservative, found in hair care products, moisturizers
	Thimerosal	Cosmetic preservative in vaccines, contact lens solution, tuberculin skin test
Resin	p-tert-butylphenol	Formaldehyde resin adhesive in leather/rubber products
Rosin	Colophony (rosin) (abietic acid)	Solder, paper products, adhesives, paints, varnishes
Rubber products	2-Meroaptobenzothiazole (MBT)	Adhesive, pesticide, animal repellents, shoe allergy
	Black rubber mix (N-Phenyl-N' Isopropyl p-phenylenediamine, N-Phenyl-N' cyclohexylphenylenediamine, N,N-diphenyl-phenylenediamine)	

Continued

TABLE 34-5 (Continued)

Common Sources	Allergen	Other Information
	Carbamates (zinc diethyldithiocarbamate, zinc dibutyldithiocarbamate)	
	Mercapto mix (4-morpholinyl-2-benzothiazyl disulfide, N-cyclohexyl-2-benzothiazole sulfenamide, 2,2-benzothiazyl disulfide)	
	Mixed dialkyl thioureas	Rubber accelerator, neoprene, tape, mouse pads, wet suits
	Tetramethylthiuram disulfide	Rubber accelerator, gloves, antimicrobial antioxidant in rubber products.
Sunscreen	Oxybenzone	Photocontact
	Padimate O (PABA)	
Turpentine	Carene	

TABLE 34-6 Common Bone Findings in Disease

Disease	Finding
Acne fulminans	Osteolytic lesions
Albright's osteodystrophy	Bradytmetacarpalism
Apert's syndrome	Synostosis
Bushke-Ollendorf syndrome	Osteopoikilosis
Cockayne's syndrome	Dwarfism
Congenital syphilis	Osteochondritis, saber shins, saddle nose, mulberry molars, Hutchinson's teeth
Conradi-Hünermann syndrome	Unilateral limb shortening, chondrodysplasia punctata
Ehler's-Danlos IX	Occipital horns
Fanconi's syndrome	Absent radius or thumb
Franceschetti-Jadassohn syndrome	Malaligned great toes
Gardner's syndrome	Craniofacial osteomatosis
Goltz's syndrome	Osteopathia striata, lobster-claw deformity, scoliosis
Gorlin's syndrome	Bifid rib, mandibular keratocysts, kyphoscoliosis, calcified falx cerebri, frontal bossing, etc.
Hallerman-Streiff syndrome	Bird-like facies, natal teeth

Continued

TABLE 34-6 (Continued)

Disease	Finding
Homocystinuria	Marfanoid habitus, genu valgum
Linear morphea	Melorheostosis
Maffucci's syndrome	Enchondromas, chondrosarcoma
Marfan's syndrome	Marfanoid habitus
McCune-Albright syndrome	Polyostotic fibrous dysplasia
MEN III	Marfanoid habitus
Multicentric reticulohistiocytosis	Mutilating arthritis
Nail-Patella syndrome	Posterior iliac horn, absent patella
Osteogenesis imperfecta	Fragile bones
Papillon-Lefèvre syndrome	Tentorial and chondroid plexus calcification

TABLE 34-7 Common Eye Findings in Disease

Condition	Eyes
Alkaptonuria	Pingueculae, Osler's sign
Allestrandini syndrome	Unilateral retinitis pigmentosa
Argyria	Blue sclera
Ataxia-telangiectasia (Louis-Bar's)	Bulbar telangiectasia
Behçet's syndrome	Retinal vasculitis, uveitis, and hypopyon
CHIME syndrome (colobomas of eye; heart defects, ichthyosiform dermatosis, mental retardation, ear defects)	Colobomas of retina
Cicatricial pemphigoid	Symblepharon
Cockayne's syndrome	Salt and pepper retinitis pigmentosa with optic atrophy
Congenital syphilis	Keratitis
Conradi-Hünemann syndrome	Asymmetric focal cataracts
Ehler's-Danlos VI	Keratoconus
Fabry's disease	Whorl-like corneal opacities, spokelike cataracts
Fanconi's syndrome	Strabismus, retinal hemorrhages
Gardner's syndrome	Congenital hypertrophy of retinal pigmented epithelium
Gaucher's disease	Pingueculae
Goltz's syndrome	Colobomas
Hallerman-Streiff syndrome	Microphthalmia, congenital cataracts, strabismus

Continued

TABLE 34-7 (Continued)

Condition	Eyes
Homocystinuria	Downward lens displacement
Incontinentia pigmenti (Bloch Sulzberger's)	Strabismus, atrophy, cataracts, optic coloboma
JXG	Hyphema, hypopyon
KID	Keratitis
Lamellar Ichthyosis	Ectropion
LEOPARD	Hypertelorism
Lipoid Proteinosis (Urbach-Wiethe)	Eyelid "string of pearls"
Marfan's syndrome	Upward lens displacement
Nail-patella syndrome	Lester iris
NF-2	Posterior subcapsular lenticular cataracts
Osteogenesis imperfecta	Blue sclera
PXE (Gronblad-Strandberg)	Angioid streak
Refsum syndrome	Salt and pepper retinitis pigmentosa
Richner-Hanhart	Pseudoherpetic keratitis
Sjögren-Larsson syndrome	Glistening dots, retinitis, pigmentosa
Tuberous sclerosis	Astrocytic hamartomas
vonRecklinghausens's (NF-1)	Lisch nodules
Waardenburg's syndrome	Dystopia, canthorum, heterchromia, irides
Wilson's disease	Kayser-Fleischer ring
X-linked ichthyosis	Posterior comma-shaped corneal opacities (Descemet's membrane)

TABLE 34-8 Common Nail Findings in Disease

Condition	Nails
5-FU and AZT	Blue lunula
Alopecia areata	Nail pits, red and spotted lunula
Apert's syndrome	One large fingernail
Argyria	Slate blue lunula
Arsenic	Mee's lines
CHF, connective tissue disease	Red lunula
Cirrhosis	Terry's nails
Coffin-Siris syndrome	Fifth-nail dystrophy

Continued

TABLE 34-8 (Continued)

Condition	Nails
Connective tissue disease and trauma	Pterygium inversum unguis
Darier-White disease	Red and white bands, V-nicking
Fe ²⁺ deficiency	Koilonychia
Hemochromatosis	Koilonychia
High fever, surgery, and meds (chemo)	Beau's lines
Hyperthyroidism	Koilonychia
Hypoalbuminemia	Muehrcke's nails
Lichen planus	Dorsal pterygium
Renal disease	Lindsay's nails
Retinoids, indinavir, and estrogen	Pyogenic granuloma
Trichinosis, endocarditis, and trauma	Splinter hemorrhages
Tuberous sclerosis	Koenen's tumor
Wilson's disease	Blue lunulae
Yellow nail syndrome	Yellow curved nails

QUIZ**Questions**

- Which of the following contact allergens would be most likely to have a persistent positive patch test?
 - Thimerosal
 - Gold
 - Nickel
 - Paraphenylenediamine
- Which desmoglein is associated with hypotrichosis?
 - Desmoglein 1
 - Desmoglein 2
 - Desmoglein 3
 - Desmoglein 4
- The gene responsible for Goltz syndrome is:
 - Myosin Va
 - PORCN
 - Endoglin
 - BP Ag2
- Griscelli syndrome results from a defect in:
 - TGF-binding proteins
 - The innate immune response
 - β -catenin
 - Melanosome transport to keratinocytes
- Oral hairy leukoplakia is related to which virus?
 - HHV6
 - EBV
 - VZV
 - Pox
- Castlemen's disease is caused by which virus?
 - HHV1
 - EBV
 - CMV
 - HHV8
- On skin biopsy, clusters of lymphocytes are seen within the epidermis in which disease?
 - Cutaneous T-cell lymphoma
 - Lipoid proteinosis
 - Ichthyosis vulgaris
 - Schwannoma
- Michaelis-Gutman Bodies are seen in:
 - Rhinoscleroma
 - CTCL
 - Atopic dermatitis
 - Malakoplakia
- The Reduviid bug is the vector for which disease?
 - Trypanosomiasis
 - Leishmaniasis
 - Cutaneous larva migrans
 - Lyme disease

10. Rickettsialpox is caused by bites from the:
 - A. House mouse (*Mus musculus*)
 - B. Rodent mite (*Allodermanyssus sanguineus*)
 - C. *Pediculosis humanus*
 - D. *Xenopsylla cheopis*
11. What is the allergen in henna tattoos?
 - A. p-Phenylenediamine
 - B. Quaternium 15
 - C. Neomycin
 - D. Ricin
12. Which of the following is NOT a formaldehyde-releasing preservative used in cosmetics and toiletries?
 - A. Diazolidinyl urea
 - B. DMDM hydantoin
 - C. Quaternium 15
 - D. Paraben
13. Which of the following nail finding is associated with lichen planus?
 - A. Triangular lunulae
 - B. Dorsal pterygium
 - C. Ventral pterygium
 - D. Blue lunulae
14. A patient with lobster-claw deformity may have which of the following bone findings?
 - A. Osteopathica striata
 - B. Bifid ribs
 - C. Occipital horns
 - D. Chondrodysplasia punctata
15. A patient with multiple polyps of the GI tract and multiple epidermoid cysts may have what eye finding?
 - A. Coloboma
 - B. Lester iris
 - C. Herpetic keratitis
 - D. Congenital hypertrophy of retinal pigment epithelium (CHRPE)
3. B. Goltz syndrome results from a defect in the gene known as PORCN, which encodes the protein, porcupine. The porcupine protein was first identified in fruit flies and named for the porcupine like spikes projecting from the fly's body. Porcupine is an important Wnt signaling protein.
4. D. Griscelli syndrome is autosomal recessive and characterized by silver gray pigmentation of hair, pigmentary dilution of skin, and increased pyogenic infections. Patients have progressive neurologic deterioration. It is caused by mutations in the gene encoding for myosin Va or RAB27a. These proteins are involved in melanosome transport to keratinocytes.
5. B. EBV infection of mucosal keratinocytes is associated with oral hairy leukoplakia. It is characterized by white plaques on the lateral surfaces of the tongue that can not be scraped off. Oral hairy leukoplakia typically occurs in HIV infected or in other immunocompromised patients.
6. D. Castleman's disease is caused by HHV8. It is a lymphoproliferative disorder that usually presents as a mediastinal mass. It can also be associated with POEMS syndrome. HSV 8 has also been associated with Kaposi's sarcoma and primary effusion lymphoma.
7. A. These lymphocyte clusters are known as Pautrier's microabscesses and are seen in CTCL.
8. D. Michaelis-Gutman bodies are seen histologically in malakoplakia. They are calcified lamellar eosinophilic bodies found in foamy macrophages. Malakoplakia is an inflammatory condition that usually affects immunocompromised people. It presents as a plaque or a nodule that usually affects the genitourinary tract but may rarely involve the skin.
9. A. American trypanosomiasis (Chagas disease) is spread by *T. cruzi* which is found in the feces of infected reduviid bugs. American Trypanosomiasis presents with an erythematous nodule at the site of inoculation. Inoculation is common through the conjunctiva which results in conjunctivitis and edema of the orbital area known as Romana's sign.
10. B. The rodent mite (*Allodermanyssus sanguineus* or *Liponyssoides sanguineus*) is the vector for rickettsialpox. The reservoir is the house mouse (*Mus musculus*). The rodent mite bite is painless and is usually not recognized by the victim. A primary lesion occurs at the site of the bite and develops into an eschar. Systemic symptoms such as fever, chills, sweats, and headache evolve 1-2

Answers

1. B. Gold allergy can be seen at all sites of jewelry contact and as eyelid dermatitis. In addition, oral lichenoid lesions can be seen. It can cause late patch test reactions and persistent patch test reactions that can last for months after testing.
2. D. Desmoglein 4. The desmoglein 4 gene (DSG4) is associated with localized autosomal recessive hypotrichosis (LAH). LAH is an autosomal recessive form of hypotrichosis affecting the scalp,

- weeks later. Two to three days later a generalized papulovesicular eruption occurs.
11. A. p-Phenylenediamine (PPD) is combined with henna to make the tattoo darker. PPD has many potential cross reactions to chemicals such as PABA, sulfonamides, thiazides, benzocaine and related anesthetics, and sulfonylureas.
 12. D. Parabens are not formaldehyde releasing and are not common causes of allergic contact dermatitis. Nonformaldehyde releasing preservatives include iodopropynyl butyl carbamate, vitamin E (alpha-tocopherol), thimersol, benzalkonium chloride, and triclosan.
 13. B. LP is associated with dorsal pterygium. Connective tissue disease can be associated with ventral pterygium.
 14. A. The question describes Goltz syndrome (focal dermal hypoplasia), which is associated with lobster-claw deformity of the fingers, short stature, and asymmetric trunk and limbs. Osteopathica striata refers to vertical striations in long bones on x-ray. Patients also have coloboma, strabismus, and microphthalmia.
 15. D. CHRPE. Patients with Gardner syndrome have polyposis with a high predisposition to adenocarcinoma. A congenital marker for diagnosis of this autosomal dominant syndrome is CHRPE. Patients also present with multiple epidermoid cysts, osteomas, desmoid tumors, odontomas, and supernumerary teeth.

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